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Ethynyl BenziodoXolone (EBX): An Exceptional Reagent for the Ethynylation of Keto-, Cyano- and Nitro- Esters.**

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Dedication ((optional))

The chemistry of acetylenes has been extensively used in organic synthesis.[1] In the last decades, the functionalization of the triple bond using metal catalysis has complemented classical acetylene chemistry with numerous addition, cyclization and cycloaddition reactions for the construction of organic molecules.[2] The exceptional properties of acetylenes have also found widespread applications in neighboring fields, such as material sciences and biochemistry.[1] To answer to this ever increasing demand for structurally diverse acetylenes, the development of new methods for their synthesis is an important task for organic chemists.[3]

Acetylene transfer reactions constitute an efficient method for the introduction of the triple bond. The SP hybridization increases the acidity of the alkyne C-H bond, allowing the easy generation of acetylide anions or metal intermediates, which have been extensively used for additions to carbonyls or imines[4] or for cross-coupling (Sonogashira) reactions.[5] In contrast, electrophilic alkynyl synthons have been much less developed,[6-8] and disconnections based on this *Umpolung* are usually not considered when planning synthesis. This constitutes a serious limitation for the synthesis of acetylenes, as for example all-carbon quaternary centers bearing a triple bond cannot be easily accessed using acetylide nucleophiles.

Reported methods for the generation of electrophilic acetylene synthons are based on the use of halogen acetylenes,[6] lead acetylide reagents[7] or alkynyliodonium salts.[8] Whereas recent progress has been achieved for the functionalization of aromatic C-H bonds,[9] the methods for the conceptually simple α-alkynylation of carbonyl groups are still limited. In particular, ethynylation reactions would be highly desirable, as they would allow direct further functionalization of the alkyne C-H bond without removal of protecting groups. To the best of our knowledge, the one-step α-ethynylation of carbonyl groups has been realized only in few examples using lead reagents[7a] or alkynyliodonium salts,[8b,8e] and the scope reported for these reactions was limited. As a result, these methods have not been broadly adopted by the organic chemistry community, and reported applications are scarce.

Recently, we discovered the exceptional reactivity of 1-[(TriIsoPropylSilyl)Ethynyl]-1,2-BenziodoXol-3(1*H*)-one (TIPS-EBX (**1**)) for metal-catalyzed alkynylation of C-H bonds and olefins.[10] Herein, we would like to report the *in situ* generation of the parent reagent, Ethynyl-1,2-BenziodoXol-3(1*H*)-one (EBX, (**3**)) from the corresponding TMS protected benziodoxolone **2** and its exceptional acetylene-transfer ability to soft enolates (Scheme 1). The simple procedure and mild reaction conditions using TBAF both as activating agent and base allowed high yields and a broad scope of substrates, including cyano and nitro esters, two classes of compounds which were never reported before. Finally, a first proof of concept for asymmetric induction has been achieved.

Scheme 1.

Prior to our work, the few methods describing the ethynylation of carbonyl compounds using hypervalent iodine reagents were all based on alkynyliodonium salts.[8b,8e] In these reports, the enolate was formed in the presence of a strong base before addition of the reagent, probably to prevent decomposition of the reagent in presence of the base. Benziodoxolone-based reagents were never used in these works.[11] As TIPS-EBX (**1**) has proven to be very stable to base and moisture in our hand, we first investigated if milder, one-pot phase-transfer conditions were possible for the alkynylation of keto-ester **4a** (Table 1, Entry 1). However, no reaction was observed with this reagent. We then decided to turn to the potentially more reactive TMS-EBX (**2**). In this case, alkynylation was observed, but the deprotected product **5a** was obtained as the major product (Entry 2). A control experiment showed that deprotection did not occur at the product

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stage under these reaction conditions. Consequently, we speculated that EBX (**3**) itself was responsible for the observed ethynylation reaction. Although both TIPS-EBX (**1**) and TMS-EBX (**2**) are bench-stable reagents, we were unable to isolate EBX (**3**), as all attempts towards silyl removal resulted into decomposition only. When KF was used as a base, free acetylene product **5a** was obtained exclusively in 87% yield (Entry 3). Although these reaction conditions worked well with cyclic keto-esters, much lower yields were obtained with other classes of substrates (*vide infra*). We then turned to TBAF as a fluoride source, but extensive decomposition of the reagent was observed at 0 °C (Entry 4). A significantly improved yield was obtained by starting the reaction at –78 °C and slowly warming up to 10 °C (71%, Entry 5). Different solvents were then examined (Entries 5-9) and alkyne **5a** was obtained in 98% yield in only 1.5 h at –78 °C in THF (Entry 9). This result demonstrated the exceptional reactivity of EBX (**3**), which allowed the alkynylation reaction to proceed under mild conditions using a simple procedure. When the same reaction was run under reported conditions with an alkynyliodonium salt via formation of the sodium enolate of **4a**,[8b] alkyne **5a** was isolated in 69% yield only (Entry 10).

Table 1.

The scope of the reaction was examined next (Table 2). Cyclic keto esters **4a-c** and phenyl-diethylmalonate (**6**) gave moderate to excellent yields in the alkynylation reaction (Entries 1-4). In contrast to cyclic keto-esters or malonates, the alkynylation of non-cyclic keto-esters has been reported only using lead reagents,[7a,7c] and there is no example of ethynylation for these more challenging substrates. Gratifyingly, the desired acetylene products were obtained in 63-93% yield for keto-esters **8a-f**, giving quaternary centers with four different carbon substituents (Entries 5-10). Both methyl (Entries 5-7) and phenyl (Entries 8-10) ketones could be used with several α-alkyl substituents, including an allyl group, which gave access to the versatile 1,5-enyne product **9f** (Entry 10). Cyano (Entries 11-12) and nitro (entries 13-16) esters were also good substrates for the reaction. Importantly, the alkynylation of theses two classes of compounds had never been reported before. The nitro substrates in particular were very sensitive compounds, and the mild conditions developed were crucial to obtain good yields.[12] A practical issue with the ethynylation reaction is the similar polarity of the starting materials and the products, which makes their separation via thin plate or column chromatography nearly impossible. Consequently, complete conversion was required to allow purification of the products. For slow reacting substrates, a better conversion was achieved when reagent **2** was added slowly at –78 °C using a syringe pump.

The obtained propargylic nitro and cyano products bearing an ester group are new structures, which have never been synthesized before. In particular, propargylic nitro compounds with a free acetylene are generally a very rare class of compounds, and their properties have never been studied in details. We consequently decided to examine the synthetic potential of product **13b** more intensively (Scheme 2).

Table 2.

The ethynylation of **12b** proceeded in 77% yield on a 4.7 mmol scale. The Cu-catalyzed [3+2] cycloaddition of **13b** with BnN_3 gave the corresponding triazole **14** in 65% yield.[13] This constituted the first example of [3+2] cycloaddition reaction of a propargyl nitro compound. Reduction of the nitro group to the amine was attempted next. To the best of our knowledge, there is only one report about the reduction of a propargylic nitro compound to the corresponding amine proceeding via the corresponding hydroxylamine **15**.[14] Although reduction to hydroxylamine **15** with Zn dust worked well, it was not possible to use the reported conditions for the reduction of the N-O bond.[14,15] Allyl amine **16** was obtained in 57% yield when Zn dust was used under more forcing conditions.[16] Gratifyingly, we found that selective reduction of the N-O bond was possible by using SmI_2 in THF/*t*BuOH.[17] Purification of the free amine was difficult, but quenching the reaction with trifluoro acetic anhydride (TFAA) allowed the isolation of the corresponding trifluoro amide **17** in good yield and purity. The obtained protected alkynyl amino acids display interesting biological activities, and only few methods have been reported for their synthesis.[18]

Scheme 2.

When optimizing the reaction, we had speculated that EBX (**3**) was the alkynylating agent. As it was not possible to isolate this reagent, we decided to monitor its formation by ^1H and ^{13}C NMR at low temperature. Treating TMS-EBX (**2**) with TBAF at –78 °C led to the immediate conversion to a new compound, which spectra were in full agreement with the structure of EBX (**3**).[19] The ^1H NMR spectrum remained unchanged when the solution was heated up to –20 °C. At this point, EBX (**3**) gradually decomposed under the generation of several not yet identified products. When a substrate was added to the EBX (**3**) solution, the only signals observable belonged to EBX (**3**), 2-iodo benzoic acid, the substrate and the ethynylation product: no further intermediate could be observed.[20]

In principle, two reaction pathways could be envisaged (Scheme 3): Addition of the enolate to the iodine atom followed by reductive elimination (pathway **A**) or conjugate addition to the alkyne, followed by a elimination and 1,2- hydride shift (pathway **B**). For both pathways, initial interaction with the carbonyl oxygen could also be envisaged. The used of ^{13}C labeled reagent **18**[21] led to product **20**, which is consistent with the 1,2-shift pathway. This mechanism had also been proposed in the case of alkynyliodonium salts.[8b] Interestingly, the opposite result was obtained in the case of metal-catalyzed alkynylation reactions using TIPS-EBX (**1**).[10]

The use of benziodoxolone-based reagents for the ethynylation reaction allowed us to increase the scope and efficiency of the reaction. Nevertheless, the obtained products are racemic, and an asymmetric method would be highly desirable. The only reported enantioselective method for the alkynylation of enolates is limited to carbonyl substituted acetylenes.[6i] Preliminary investigations using the phase-transfer conditions developed by Jørgensen[6] in fact led to a moderate asymmetric induction (Equation 1). Interestingly, the use of alkynyliodonium salts led to the formation of racemic products in this case, highlighting a further advantage of EBX (**3**) as electrophilic ethynylation reagent.

Scheme 3.

Equation 1.

In conclusion, we have reported the first use of benziodoxolone-based hypervalent iodine reagents for the ethynylation of activated carbonyl compounds. The reactive EBX (**3**) was generated from the bench-stable TMS-EBX (**2**) in the presence of TBAF under mild conditions. The high acetylene transfer ability of **3** resulted in good yield for ethynylation reactions. For the first time, acetylene transfer to non-cyclic keto- and cyano- esters was achieved, which gave access to quaternary centers with four different carbon substituents, a synthetically challenging class of compounds in organic chemistry. Unprecedented alkyne substituted nitro esters were synthesized, and methods for their transformation to the corresponding protected amino acids were developed. The reaction was shown to proceed via a 1,2-shift mechanism similar to the one proposed for alkynyliodonium salts. Finally, we demonstrated that asymmetric induction was possible under phase-transfer conditions. The simplicity of the reported method, as well as its broad scope, greatly enhances the utility of electrophilic alkyne synthons in organic chemistry and is expected to stimulate chemists to use more routinely an *Umpolung* approach for the synthesis of acetylenes. Application of benziodoxolone reagents for the alkynylation of other nucleophiles, as well as improvement of the asymmetric induction are currently under investigation in our laboratory.

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Keywords: Alkynylation · Hypervalent Iodine · Reactivity · Umpolung · Quaternary Center.

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[12] When the ethynylation of substrate **12b** was done using an alkynyliodonium salt following a reported procedure,[8b] only 46% yield of **13b** was obtained. Using phase-transfer conditions reported in Entry 3, Table 1 for substrate **12c** gave **13c** in only 24% yield.

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[19] In particular, a acetylene C-H signal was now visible at 3.50 ppm. See Figure S1 in supporting information.

[20] In case of slower reacting substrates, partial decomposition of EBX was also observed.

[21] For reason of synthetic accessibility, the labeled TIPS-EBX reagent **18** was used. Generally, TIPS-EBX (**1**) was as efficient as TMS-EBX (**2**) as reagent precursor, although silyl group removal was slightly slower.

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Scheme and figure legends:

Scheme 1. Alkynylation of Soft Enolates with EBX (3).

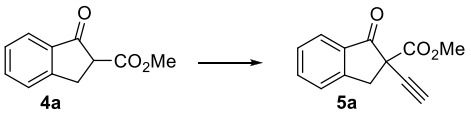
Scheme 2. Scale up of the synthesis and functionalization of **13b**. Reaction conditions: a) 1.3 equiv **2**, 1.3 equiv TBAF, THF, -78 °C, 77%; b) 1 equiv BnN_3, 5 mol % $CuSO_4$, 10 mol % Na ascorbate, *t*BuOH/H_2O 1:1, 60 °C, 65%; c) Zn, 1 N HCl/AcOH, 0 °C, 57%; d) Zn, NH_4Cl, EtOH/H_2O 1:1, 0°C, 94%; e) SmI_2, THF, *t*BuOH, then TFAA, 67%.

Scheme 3. Possible mechanisms for the ethynylation reaction and labeling experiment (Ar = phenyl-2-carboxylate).

Equation 1.

Tables:

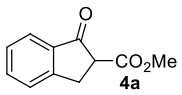
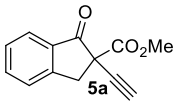
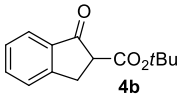
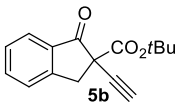
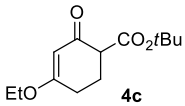
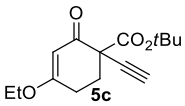
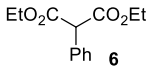
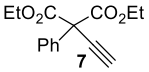
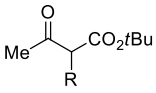
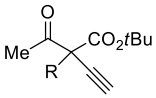
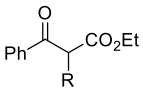
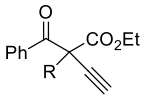
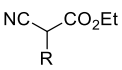
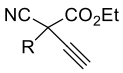
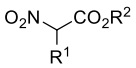
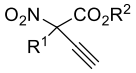
Table 1. Alkynylation of Keto-Ester **4a**.



Entry	Reaction conditions[a]	Solvent	Yield
1	**1**, sat. K_2CO_3, $Me_4N^+Cl^-$, 0 °C	toluene	n.r.[b]
2	**2**, sat. K_2CO_3, $Me_4N^+Cl^-$, 0 °C	toluene	<80%[c]
3	**2**, sat. KF, $Me_4N^+Cl^-$, 0 °C	toluene	87%
4	**2**, TBAF, 0 °C	toluene	dec.
5	**2**, TBAF, –78 to 10 °C, 12 h	toluene	71%
6	**2**, TBAF, –78 to 10 °C, 12 h	Et_2O	49%
7	**2**, TBAF, –78 to 10 °C, 12 h	*i*PrOH	<90%[c]
8	**2**, TBAF, –78 °C, 3 h	CH_2Cl_2	78%
9	**2**, TBAF, –78 °C, 1.5 h	THF	98%
10	Ochiai's conditions[8b]	THF	69%

[a] Reactions under phase-transfer conditions (Entries 1-3): 0.3 mmol substrate, 10 mol % $Me_4N^+Cl^-$, 1.3 equiv reagent, toluene/saturated base solution (5 mL/1.5 mL). Reactions with TBAF: 0.4 mmol substrate, 1.3 equiv TBAF, 1.3 equiv reagent, solvent (3.3 mL). [b] n.r. = no reaction. [c] Product **5a** could not be separated from non-identified impurities.

Table 2. Scope of the Alkynylation of Activated Carbonyls

Entry	Substrate	Product	Isolated Yield[a]
1	 **4a**	 **5a**	98%
2	 **4b**	 **5b**	94%
3	 **4c**	 **5c**	50%[b]
4	 **6**	 **7**	95%[c]
			
5	R = Me (**8a**)	**9a**	90%
6	R = Et (**8b**)	**9b**	63%[b]
7	R = Bn (**8c**)	**9c**	77%
			
8	R = Me (**8d**)	**9d**	83%
9	R = Bn (**8e**)	**9e**	93%[b,c]
10	R = allyl (**8f**)	**9f**	88%[b]
			
11	R = Bn (**10a**)	**11a**	90%
12	R = 4-Br-Bn (**10b**)	**11b**	75%
			
13	R^1 = Me, R^2 = Et (**12a**)	**13a**	75%
14	R^1 = Bn, R^2 = Et (**12b**)	**13b**	93%
15	R^1 = Ph, R^2 = Me (**12c**)	**13c**	80%
16	R^1 = Ph, R^2 = ^{t}Bu (**12d**)	**13d**	85%

[a] 0.4 mmol substrate, 1.3 equiv TBAF, 1.3 equiv reagent **2**, at –78 °C or from –78 °C to 10 °C, 1-20 h, solvent (3.3 mL) (see supporting information for exact reaction time and temperature) [b] The reagent was slowly added as a solution (THF/CH_2Cl_2 5:1) over 10 h. [c] The reaction was run with 1.8 equiv of reagent **2**.

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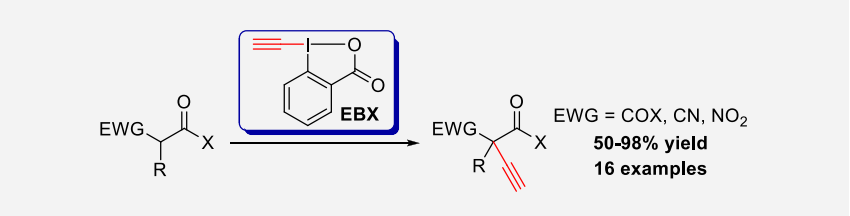
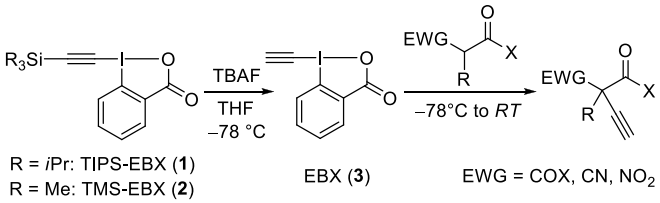
Ethynyl BenziodoXolone (EBX): An Exceptional Reagent for the Ethynylation of Keto-, Cyano- and Nitro- Esters.



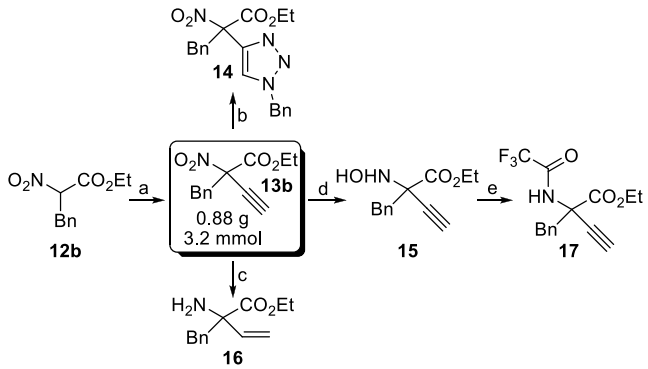
Hot alkyne! The *in situ* generation of Ethynyl-1,2-BenziodoXol-3(1*H*)-one (EBX) from the corresponding silyl protected reagent using TBAF is reported. EBX displayed exceptional acetylene transfer ability to stabilized enolates, even at –78 °C. The mild reaction conditions allowed the first ethynylation reactions of linear keto, cyano and nitro esters in high yields to give all-carbon quaternary centers or non-natural amino acids after selective reduction of the nitro group.

Keywords: Alkynylation · Hypervalent Iodine · Reactivity · Umpolung · Quaternary Center.

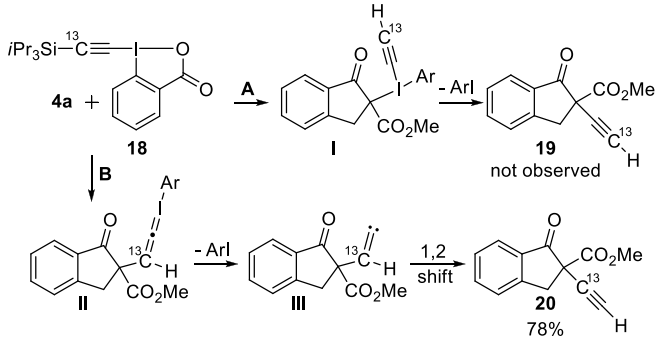
Graphical materials:



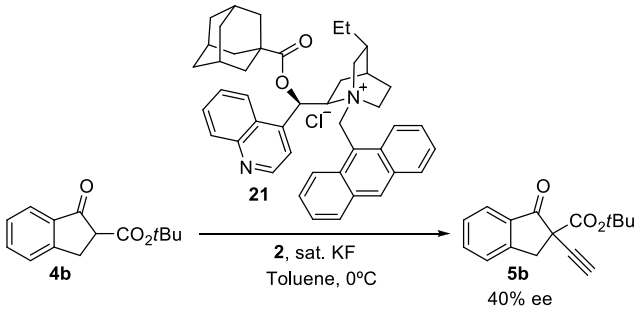
Scheme 1. Alkynylation of Soft Enolates with EBX (3).



Scheme 2. Scale up of the synthesis and functionalization of **13b**. Reaction conditions: a) 1.3 equiv **2**, 1.3 equiv TBAF, THF, -78 °C, 77%; b) 1 equiv BnN_3, 5 mol % $CuSO_4$, 10 mol % Na ascorbate, *t*BuOH/H_2O 1:1, 60 °C, 65%; c) Zn, 1 N HCl/AcOH, 0 °C, 57%; d) Zn, NH_4Cl, EtOH/H_2O 1:1, 0°C, 94%; e) SmI_2, THF, *t*BuOH, then TFAA, 67%.

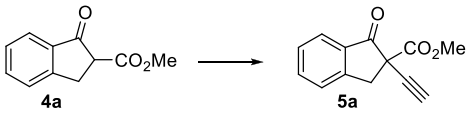


Scheme 3. Possible mechanisms for the ethynylation reaction and labeling experiment (Ar = phenyl-2-carboxylate).

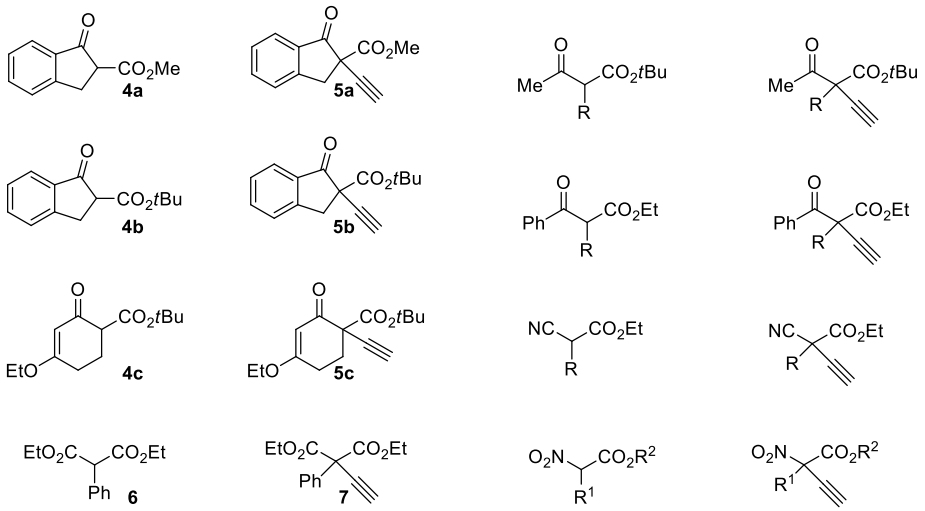


Equation 1.

Draws for Table 1. Alkynylation of Keto-Ester **4a**.



Draws for Table 2. Scope of the Alkynylation of Activated Carbonyls



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1. General Methods

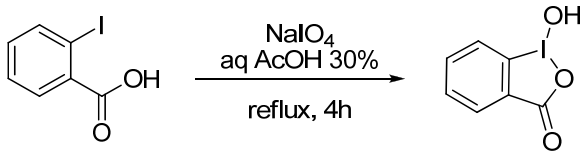
All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, *Karl-Fischer* titration). NEt_3 and pyridine were distilled under nitrogen from KOH. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem, Maybrige, TCI or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. Macherey -Nagel silica 40-63, 60 Å was deactivated using EtN_3 (2% v/v) in the solvents indicated as eluent and the solvents were removed under reduce pressure.TLC was performed on Merck silica gel 60 F_{254} TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz or Brucker AV-400 400MHZ spectrometer in chloroform-d, CD_2Cl_2-d_2, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal CD_2Cl_2 signal at 5.33 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration; interpretation).^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz or Brucker AV-400 400MHZ spectrometer in chloroform-d, CD_2Cl_2-d_2, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal CD_2Cl_2 signal at 53.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = *weak*, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. Elemental analysis was performed at the elemental analysis of ISIC at EPFL. HPLC measurements were done on a JASCO HPLC system with an AS 2055 Autosampler, a PV 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAC IC column from DAICEL Chemical industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

Caution: Hypervalent iodine reagents are high energy compounds. Although no problem has ever been encountered in this work, adequate care (safety shield) has to be taken, especially during large scale synthesis of reagents.

2. Preparation of Reagents and Substrates

2.1 Preparation of Reagents

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (23)



22 **23**

Following the reported procedure,[1] $NaIO_4$ (7.24 g, 33.8 mmol, 1.05 equiv) and 2-iodobenzoic acid (**22**) (8.00 g, 32.2 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (48 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to RT, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 20 mL) and acetone (3 x 20 mL), and air-dried in the dark to give the pure product **23** (8.3 g, 31 mmol, 98%) as a colorless solid.

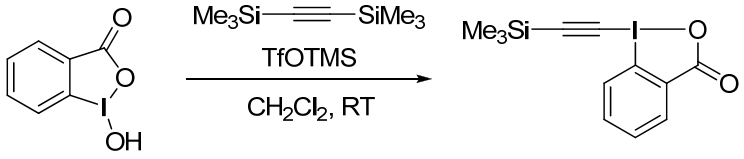
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1 H; Ar*H*), 7.97 (m, 1 H; Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1 H; Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1 H; Ar*H*);

^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4;

IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m).

The characterization data for compound **23** corresponded to the reported values.[1]

1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX, 2)



23 **2**

Following a slight modification of the reported procedure,[2] trimethylsilyl triflate (5.54 mL, 30.7 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**23**) (7.36 g, 28.0 mmol, 1 equiv) in CH_2Cl_2 (85 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of bis(trimethylsilyl)acetylene (6.98 mL, 30.7 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at RT, during this time a white solid was formed. A saturated solution of $NaHCO_3$ was then added and the mixture was stirred vigorously until completely solubilization of the white solid. The two layers were separated and the combined organic extracts were washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under reduce pressure. Recrystallization from acetonitrile (5 mL) afforded **2** (7.17 g, 20.8 mmol, 74%) as a colorless solid.

[1] L. Kraszkiewicz, L. Skulski, *Arkivoc*. **2003**, *6*, 120.
[2] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547.

Mp: 143-145°C (dec);

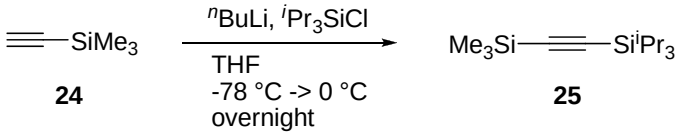
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J*= 6.4, 1.9 Hz, 1 H; Ar*H*), 8.19 (m, 1 H; Ar*H*), 7.78 (m, 2 H; Ar*H*), 0.32 (s, 9 H; TMS);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.9, 132.6, 131.7, 131.4, 126.1, 117.2, 115.4, 64.2, -0.5;

IR ν 3389 (w), 2967 (w), 1617 (s), 1609 (s), 1562 (m), 1440 (w), 1350 (m), 1304 (w), 1254 (w), 1246 (w), 1112 (w), 1008 (w), 852 (s), 746 (m), 698 (m), 639 (m).

The characterization data for compound **2** corresponded to the reported values.[2]

Tri*iso*-propylsilyl trimethylsilylacetylene (25)



24 **25**

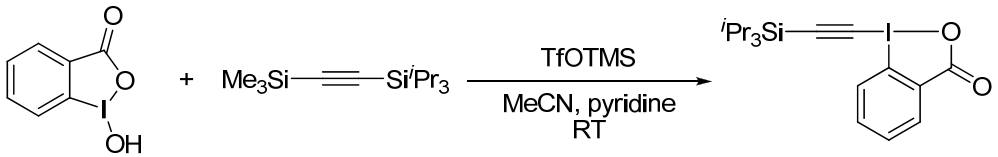
Following a reported procedure,[3] *n*-butyllithium (2.5 M in hexanes, 12.0 mL, 29.9 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**24**) (3.0 g, 30 mmol, 1.0 equiv) in THF (48 mL) at –78 °C. The mixture was then warmed to 0 °C and stirred for 5 min. The mixture was then cooled back to –78 °C and chlorotri*iso*-propylsilane (6.4 mL, 30 mmol, 1.0 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (40 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 60 mL). The organic layer was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by Kugelrohr distillation (bp = 56-57°C, p = 0.25 mmHg) to yield **25** (7.16 g, 28.0 mmol, 92% yield) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (m, 21 H; TIPS), 0.18 (s, 9 H; TMS);

IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m).

Characterization data of **25** corresponded to the literature values.[3]

1-[(Tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, 1)



23 **25** **1**

Following a reported procedure,[2] trimethylsilyltriflate (3.6 mL, 20 mmol, 1.1 equiv, freshly distilled) was added dropwise to a stirred solution of 2-iodosylbenzoic acid (**23**) (4.7 g, 18 mmol, 1.0 equiv) in acetonitrile (140 mL). (Trimethylsilyl)(tri*iso*-propylsilyl)acetylene (**25**) (5.0 g, 20 mmol, 1.1 equiv) was then added dropwise, followed, after 15 min, by the addition of pyridine (1.5 mL, 20 mmol, 1.1 equiv). The mixture was stirred 10 min. The solvent was then removed under reduced pressure and the yellow crude oil

[3] C J. Helal, P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 10938.

was dissolved in dichloromethane (50 mL). The organic layer was washed with 1 M HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2 x 50 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (*ca* 35 mL) afforded **1** (6.3 g, 15 mmol, 83%) as a colorless solid.

Mp (Dec.) 170-176°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (m, 1 H; Ar*H*), 8.29 (m, 1 H; Ar*H*), 7.77 (m, 2 H; Ar*H*), 1.16 (m, 21 H; TIPS);

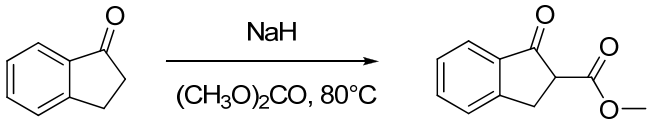
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1;

IR ν 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m).

Characterization data of **1** corresponded to the literature values.[2]

2.2 Preparation of Substrates

Methyl 1-oxo-2-indanecarboxylate (4a)



26 **4a**

Following the reported procedure,[4] a suspension of NaH (6.64 g, 60% in mineral oil, 166 mmol, 2.2 equiv) in dimethyl carbonate (20 mL) was charged in a 250 mL two-neck flask. 1-Indanone (**26**) (10.0 g, 75.5 mmol, 1 equiv) in dimethyl carbonate (70 mL) was added dropwise and the resulting mixture was refluxed at 80 °C for 2 h. After cooling to RT, 200 mL of water was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ filtered and concentrated under reduce pressure. The brown residual oil was purified by flash chromatography (PET/EtOAc 4:1) to afford **4a** (10.5 g, 55.4 mmol, 73%) as orange solid.

Mp (Dec.) 139-145°C;

R_f 0.3 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) Keto-enol (6:1) δ 10.35 (br s, 0.16 H; O*H*-enol),), 7.76 (d, *J* = 7.6 Hz, 1 H; Ar*H*), 7.61 (t, *J* = 7.5 Hz, 1 H; Ar*H*), 7.49 (d, *J* = 7.7 Hz, 1 H; Ar*H*), 7.38 (t, *J* = 7.5 Hz, 1 H; Ar*H*), 3.84 (s, 0.5 H; OC*H*$_3$-enol), 3.78 (s, 3 H; OC*H*$_3$), 3.73 (dd, *J* = 8.2, 4.0 Hz, 1H; C*H*CO), 3.55 (dd, *J* = 17.3, 3.8 Hz, 1 H; C*H*$_2$), 3.50 (s, 0.3 H; C*H*$_2$-enol), 3.37 (dd, *J* = 17.3, 8.3 Hz, 1 H; C*H*$_2$);

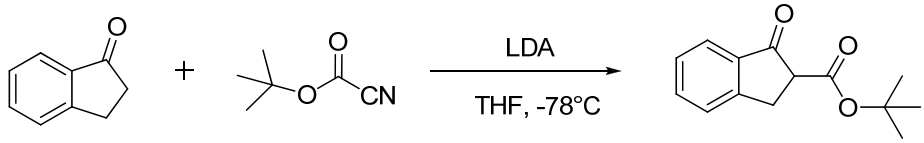
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 169.4, 153.5, 135.3, 135.0, 129.3, 127.7, 126.7, 126.4, 124.6, 124.5, 120.6, 53.0, 51.1, 32.4, 30.1;

[4] K. Van Emelen, T. De Wit, G. J. Hoornaert, F. Compernolle, *Tetrahedron.* **2002**, *58*, 4225.

IR ν 3033 (w), 2954 (w), 2848 (w), 2360 (w), 2342 (w), 1742 (s), 1711 (s), 1653 (m), 1609 (m), 1574 (m), 1464 (m), 1436 (m), 1328 (m), 1298 (m), 1261 (m), 1209 (s), 1154 (s), 1095 (w), 989 (m), 963 (w), 850 (w), 764 (s), 722 (w), 683 (w).

Characterization data of **4a** corresponded to the literature values.[4]

***tert*Butyl 1-oxoindan-2-carboxylate (4b)**



26 **27** **4b**

Following the reported procedure,[5] *n*-butyllithium (2.5 M, 3.30 mL, 8.32 mmol, 1.1 equiv) was slowly added to a cooled (-78 °C) mixture of diisopropylamine (1.17 mL, 8.32 mmol, 1.1 equiv) in dried THF (12 mL). The resulting mixture was placed in an ice-bath and stirred at 0 °C for 0.5 h. After this time, the mixture was cooled at -78 °C and a solution of 1-indanone (**26**) (1.00 g, 7.56 mmol, 1 equiv) in THF (15 mL) was added and stirred 30 min at -78 °C. *tert*Butyl cyanoformate (**27**) (1.06 g, 8.32 mmol, 1.1 equiv) in THF (5 mL) was added. The resulting mixture was stirred 1 h at -78 °C, and then allowed to warm to RT. The reaction was quenched with sat. NH_4Cl solution, the aqueous layer was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduce pressure. The resulting crude mixture was purified by flash chromatography (Hexane/EtOAc, 95:5) to give **4b** as pink oil (663 mg, 2.85 mmol, 40%).

R_f 0.6 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H; Ar*H*), 7.58 (t, *J* = 7.2 Hz, 1H; Ar*H*), 7.47 (d, *J* = 7.5 Hz, 1H; Ar*H*), 7.35 (t, *J* = 7.2 Hz, 1H; Ar*H*), 3.60 (dd, *J* = 8.2, 4.0 Hz, 1 H; C*H*CO), 3.47 (dd, *J* = 17.2, 3.9 Hz,1 H; CH_2), 3.31 (dd, 1 H, *J* = 17.2, 8.2 Hz, 1 H; CH_2), 1.47 (s, 9H; OC(CH_3)$_3$);

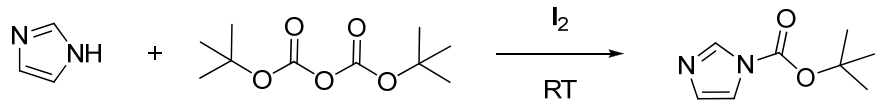
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 168.2, 153.6, 135.3, 135.1, 127.6, 126.4, 124.4, 81.9, 54.3, 30.2, 27.9;

IR 3073 (w), 2979 (w), 2933 (w), 2870 (w), 2359 (w), 2342 (w), 1713 (s), 1645 (w), 1608 (w), 1574 (w), 1464 (w), 1393 (w), 1369 (m), 1329 (w), 1293 (w), 1270 (w), 1254 (w), 1211 (w), 1149 (s), 1092 (w), 1014 (w), 989 (w), 897 (w), 845 (w), 773 (w), 759 (w), 740 (m), 680 (w), 630 (w);

Characterization data of **4b** corresponded to the literature values.[6]

[5] T. B. Poulsen, L. Bernardi, J. Aleman, J. Overgaard, K. A. Jorgensen, *J. Am. Chem. Soc.* **2007**, *129*, 441.
[6] T. A. Moss, D. R. Fenwick, D. J. Dixon, *J. Am. Chem. Soc.* **2008**, *130*, 10076.

***tert*-Butyl 1*H*-imidazole-1-carboxylate (30)**



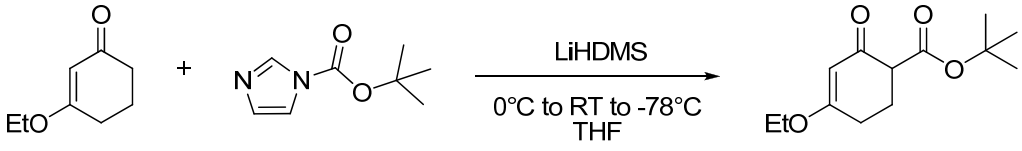
28 **29** **30**

Following the reported procedure,[7] I_2 (584 mg, 2.30 mmol, 0.1 equiv) was added to a stirred solution of 1*H*-imidazole (**28**) (1.56 g, 23.0 mmol, 1 equiv) and $(Boc)_2O$ (**29**) (5.00 g, 23.0 mmol, 1 equiv) under solvent-free conditions at RT. The reaction mixture was stirred 20 min at RT and then Et_2O (20 mL) was added. The mixture was washed with $Na_2S_2O_3$ (5%, 30 mL), sat. $NaHCO_3$ and dried over Na_2SO_4. The solution was concentrated and purified by flash chromatography (Hexane/EtOAc 40:1, 30:1, 20:1) to afford *tert*-butyl 1*H*-imidazole-1-carboxylate (**30**) (3.25 g, 19.3 mmol, 84%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1 H; NC*H*N), 7.15 (s, 1 H; C*H*), 6.82 (s, 1 H; C*H*), 1.43 (s, 9H; OC(CH_3)$_3$).

Characterization data of **30** corresponded to the literature values.[7]

***tert*-Butyl 4-ethoxy-2-oxocyclohex-3-enecarboxylate (4c)**



31 **30** **4c**

n-Butyllithium (2.5 M, 3.50 mL, 8.75 mmol, 2.5 equiv) was slowly added during 10 min to a stirred mixture of hexamethyldisilazane (1.86 mL, 8.75 mmol, 2.5 equiv) in dried THF (8.25 mL) at 0 °C. The resulting mixture was stirred at RT for 0.5 h. After this time, the mixture was cooled to -78 °C and 3-ethoxycyclohex-2-enone (**31**) (0.47 mL, 3.5 mmol, 1 equiv) was added, and the mixture was stirred at -78 °C for 10 min, then 15 min at RT. The mixture was then cooled to -78 °C and *tert*-butyl 1*H*-imidazole-1-carboxylate (**30**) (880 mg, 5.25 mmol, 1.5 equiv) was added and the resulting mixture was allowed to gradually reach RT. After stirring for 30 min, the reaction was quenched with sat. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting crude mixture was purified by flash chromatography (Hexane/AcOEt 10:1) affording compound **4c** (633 mg, 2.64 mmol, 75%) as a white solid.

R_f 0.25 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1 H; C=CC*H*), 3.90 (m, 2 H; OCH_2), 3.20 (dd, *J* = 8.5, 5.1 Hz, 1 H; C*H*CO), 2.53 (m, 1 H; CH_2), 2.41 (m, 1 H; CH_2), 2.28 (m, 1 H; CH_2), 2.13 (m, 1 H; CH_2), 1.46 (s, 9 H; OC(CH_3)$_3$), 1.36 (t, *J* = 7.0 Hz, 3 H ; OCH$_2$CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 177.3, 169.6, 102.1, 81.5, 64.4, 53.1, 28.0, 27.3, 24.3, 14.1;

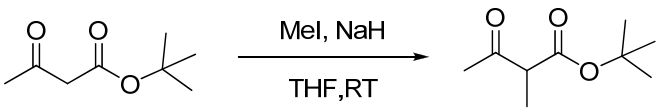
IR ν 2982 (w), 2940 (w), 2366 (w), 2338 (w), 1731 (s), 1665 (m), 1607 (s), 1478 (w), 1457 (w), 1367 (m), 1318 (w), 1287 (w), 1249 (w), 1195 (m), 1150 (s), 1112 (w), 1088 (w), 1029 (w), 1006 (w), 915 (w), 911 (w), 847 (w), 781 (w), 738 (m), 656 (w), 612 (w);

[7] R. Varala, S. Nuvula, S. R. Adapa, *J. Org. Chem.* **2006**, *71*, 8283.

HRMS(ESI) calcd for $C_{13}H_{21}O_4^+$ (M+H) 241.1440, found 241.1431.

Characterization data of **4c** corresponded to the literature values.[5]

***tert*-Butyl 2-methyl-3-oxobutanoate (8a)**



32 **8a**

Following a slightly modified procedure,[8] *tert*Butyl acetoacetate (**32**) (16.6 mL, 100 mmol, 1 equiv) was added dropwise to a suspension of NaH (2.4 g, 60% in mineral oil, 0.10 mol, 1 equiv) in THF (150 mL). The resulting mixture was stirred at RT until gas evolution finished and then methyl iodide (6.2 mL, 0.10 mol, 1 equiv) was added. The reaction mixture was stirred for 6.5 h followed by the addition of methyl iodide (3.1 mL, 50 mmol, 0.5 equiv). The mixture was additionally stirred 13.5 h at RT. After this time, the reaction was quenched with sat. NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated at reduced pressure. The resulting yellow liquid residue was purified by flash chromatography (Hexane/AcOEt 50:1) to afford **8a** (3.40 g, 19.7 mmol, 20%) as a colorless liquid.

R_f 0.59 (PET/EtOAc 4:1, UV/Anisaldehyde);

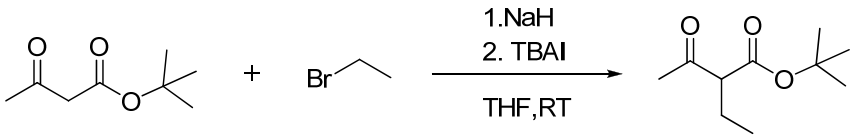
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (q, *J* = 7.1 Hz, 1 H; C*H*), 2.19 (s, 3 H; CH_3CO), 1.42 (s, 9 H; OC(CH_3)$_3$), 1.24 (d, *J* = 7.1 Hz, 3 H; CH_3CH);

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 169.6, 81.7, 54.6, 28.3, 27.8, 12.6;

IR ν 2982 (m), 2939 (w), 2363 (w), 2337 (w), 1737 (s), 1714 (s), 1648 (w), 1457 (w), 1369 (m), 1332 (w), 1253 (m), 1146 (s), 1078 (w), 1043 (w), 954 (w), 901 (w), 847 (m), 735 (w), 660 (w).

Characterization data of **8a** corresponded to the literature values.[9]

***tert*-Butyl 2-ethyl-3-oxobutanoate (8b)**



32 **33** **8b**

Following a slightly modified procedure,[8] a suspension of NaH (2.4 g, 60% in mineral oil, 0.10 mol, 1 equiv) in 150 mL of THF was charged in a 250 mL two-neck flask. *tert*Butyl acetoacetate (**32**) (16.6 mL, 100 mmol, 1 equiv) was added dropwise and the resulting mixture was stirred at RT until gas evolution finished. Ethyl bromide (**33**) (7.5 mL, 0.10 mol, 1 equiv) was then added and the reaction mixture was stirred for 1.5 h. Tetrabutylammonium iodide (3.7 g, 10 mmol, 0.1 equiv) was added and the reaction mixture was additionally stirred for 20 h. After this time, ethyl bromide (**33**) (3.7 mL, 50 mmol, 0.5 equiv)

[8] Guijarro, D.; Yus, M. *Tetrahedron* **1995**, *51*, 11445.
[9] C. Palomo, M. Olarbide, J. M. Garcia, P. Banuelos, J. M. Odriozola, J. Razkin, A. Linden, *Org. Lett.* **2008**, *10*, 2637.

was added then the mixture was stirred at 90 °C under reflux for 2 h. The reaction mixture was hydrolyzed with sat. NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting yellow liquid residue was purified by flash chromatography (Hexane/AcOEt 50:1) affording **8b** (11.3 g, 60.6 mmol, 60%) as a colorless liquid.

R_f 0.78 (PET/EtOAc 4:1, UV/Anisaldehyde);

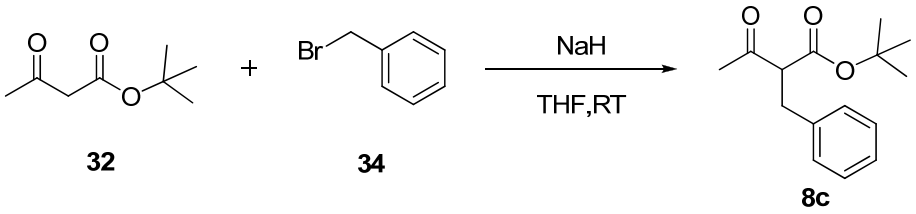
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (t, *J* = 7.4 Hz, 1 H; C*H*), 2.15 (s, 3 H; CH_3CO), 1.77 (m, 2 H; CH_2), 1.41 (s, 9 H; OC(CH_3)$_3$), 0.87 (t, *J* = 7.4 Hz, 3 H; CH_3CH$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 168.9, 81.5, 62.4, 28.6, 27.8, 21.4, 11.7;

IR ν 2975 (m), 2936 (w), 2880 (w), 2362 (w), 2337 (w), 1739 (s), 1714 (s), 1643 (w), 1461 (w), 1393 (w), 1367 (m), 1257 (w), 1210 (w), 1145 (s), 1088 (w), 1049 (w), 948 (w), 847 (w), 811 (w), 732 (w), 677 (w), 656 (w).

Characterization data of **8b** corresponded to the literature values.[9]

***tert*-Butyl 2-benzyl-3-oxobutanoate (8c)**



32 **34** **8c**

Following a slightly modified reported procedure,[8] a suspension of NaH (6.0 g, 60% in mineral oil, 0.25 mol, 1 equiv) in 375 mL of THF was charged in a 500 mL two-neck flask. *tert*Butyl acetoacetate (**32**) (41.5 mL, 250 mmol, 1 equiv) was added dropwise and the resulting mixture was stirred at RT until gas evolution finished. Benzyl bromide (**34**) (30 mL, 0.25 mol, 1 equiv) was then added and the reaction mixture was stirred for 1 h. The reaction was quenched with sat. NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure, giving an oily residue. Distillation (bp = 105 °C, p = $5.4 \cdot 10^{-1}$ mbar) afforded **8c** (24.2 g, 97.4 mmol, 39%) as a colorless liquid.

R_f 0.53 (PET/EtOAc 4:1, UV/Anisaldehyde);

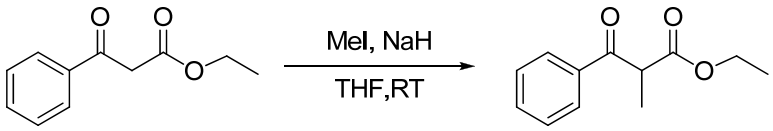
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2 H; Ar*H*), 7.19 (m, 3 H; Ar*H*), 3.71 (t, *J* = 7.9 Hz, 1 H; C*H*), 3.12 (m, 2 H; CH_2), 2.18 (s, 3 H; CH_3), 1.39 (s, 9 H; OC(CH_3)$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4, 168.0, 138.2, 128.6, 128.2, 126.3, 81.7, 62.0, 33.7, 29.2, 27.6;

IR ν 3087 (w), 3064 (w), 3031 (w), 3004 (w), 2979 (w), 2934 (w), 2898 (w), 2361 (w), 2343 (w), 1733 (s), 1715 (s), 1642 (w), 1605 (w), 1497 (w), 1456 (w), 1376 (w), 1369 (m), 1253 (m), 1226 (m), 1141 (s), 1083 (w), 1060 (w), 1032 (w), 984 (w), 957 (w), 845 (m), 747 (m), 730 (w), 701 (s), 676 (w).

Characterization data of **8c** corresponded to the literature values.[9]

Ethyl 2-methyl-3-oxo-3-phenylpropanoate (8d)



35 **8d**

Following a slightly modified procedure,[8] ethyl benzoyl acetate (**35**) (1.7 mL, 10 mmol, 1 equiv) was added dropwise to a suspension of NaH (0.24 g, 60% in mineral oil, 10 mmol, 1 equiv) in THF (15 mL). The resulting mixture was stirred at RT until gas evolution finished and then methyl iodide (0.62 mL, 10 mmol, 1 equiv) was added. The reaction mixture was stirred for 20 h at RT. The reaction was quenched with sat. NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Product **8d** was obtained without purification (2.0 g, 9.7 mmol, 100%) as orange oil.

R_f 0.68 (PET/EtOAc 4:1, UV/Anisaldehyde);

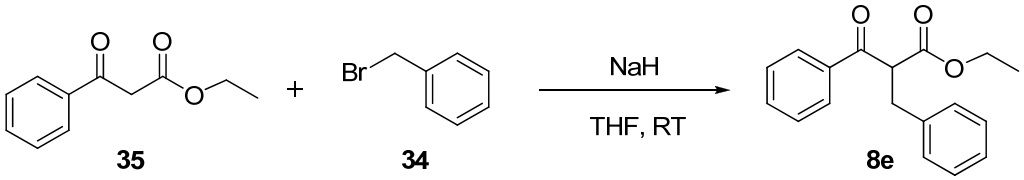
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.1 Hz, 2 H; Ar*H*), 7.58 (m, 1 H; Ar*H*), 7.47 (t, *J* = 7.9 Hz, 2H; Ar*H*), 4.37 (q, *J* = 7.1 Hz, 1 H; C*H*), 4.14 (q, *J* = 7.1 Hz, 2 H; CH_2), 1.49 (d, *J* = 7.1 Hz, 3H; CH_3CH), 1.16 (t, *J* = 7.1 Hz, 3 H; CH_3CH_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 170.3, 135.4, 133.0, 128.2, 128.1, 60.7, 47.7, 13.4, 13.2;

IR ν 3065 (w), 2987 (w), 2943 (w), 2904 (w), 2876 (w), 2360 (w), 2337 (w), 1737 (s), 1687 (s), 1597 (w), 1452 (m), 1373 (m), 1334 (m), 1307 (m), 1222 (s), 1189 (s), 1088 (m), 1034 (m), 967 (m), 914 (w), 862 (w), 787 (w), 732 (m), 693 (m), 661 (w).

Characterization data of **8d** corresponded to the literature values.[10]

Ethyl 2-benzyl-3-oxo-3-phenylpropanoate (8e)



35 **34** **8e**

Following a slightly modified procedure,[8] ethyl benzoyl acetate (**35**) (1.2 mL, 7.0 mmol, 1 equiv) was added dropwise to a suspension of NaH (0.17 g, 60% in mineral oil, 7.0 mmol, 1 equiv) in THF (11 mL) . The resulting mixture was stirred at RT until gas evolution finished and then benzyl bromide (**34**) (0.84 mL, 7.0 mmol, 1 equiv) was added. The reaction mixture was stirred for 20 h at RT. After this time, the reaction mixture was quenched with sat. NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting yellow liquid residue was purified by flash chromatography (Hexane/AcOEt 20:1) to afford **8e** (1.52 g, 5.38 mmol, 76%) as a colorless liquid.

R_f 0.47 (PET/EtOAc 4:1, UV/Anisaldehyde);

[10] C. V. Galliford, K. A. Scheidt, *Chem. Commun.* **2008**, 1926.

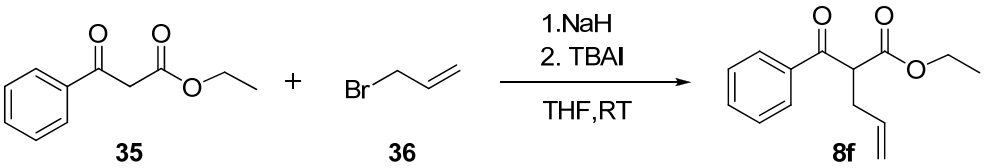
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.4 Hz, 2 H; Ar*H*), 7.59 (m, 1 H; Ar*H*), 7.47 (t, *J* = 7.9 Hz, 2 H; Ar*H*), 7.25 (m, 5 H; Ar*H*), 4.65 (t, *J* = 7.3 Hz, 1 H; C*H*), 4.12 (m, 2 H; OCH_2), 3.36 (m, 2 H; CH_2CH), 1.14 (t, *J* = 7.2 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 168.8, 138.2, 133.1, 133.1, 128.5, 128.3, 128.2, 128.0, 126.2, 61.0, 55.6, 34.3, 13.3;

IR 3087 (w), 3064 (w), 3030 (w), 2984 (w), 2937 (w), 2905 (w), 2871 (w), 2360 (m), 2342 (w), 1733 (s), 1685 (s), 1597 (m), 1582 (w), 1496 (m), 1449 (m), 1370 (w), 1308 (w), 1271 (w), 1232 (m), 1184 (w), 1149 (m), 1098 (w), 1082 (w), 1056 (w), 1031 (m), 944 (w), 894 (w), 855 (w), 777 (m), 738 (m), 693 (s).

Characterization data of **8e** corresponded to the literature values.[10]

Ethyl 2-benzoylpent-4-enoate (8f)



35 **36** **8f**

Following a slightly modified procedure,[8] ethyl benzoyl acetate (**35**) (1.5 mL, 8.6 mmol, 1 equiv) was added dropwise to a suspension of NaH (0.21 g, 60% in mineral oil, 8.6 mmol, 1 equiv) in THF (13 mL) . The resulting mixture was stirred at RT until gas evolution finished and then allyl bromide (**36**) (0.74 mL, 8.6 mmol, 1 equiv) was added. The reaction mixture was stirred for 18 h followed by the addition of allyl bromide (**36**) (0.74 mL, 8.6 mmol, 1 equiv) and then was additionally stirred 2.5 h at RT. After this time, tetrabutylammonium iodide (0.16 g, 0.43 mmol, 0.05 equiv) was added. After 2 h, the reaction mixture was treated with sat. NH_4Cl and the aqueous layer was extracted with ethyl acetate (3x10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting yellow liquid residue was purified by flash chromatography (Hexane/AcOEt 30:1) to afford **8f** (1.43 g, 6.15 mmol, 72%) as a colorless liquid.

R_f 0.65 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.2 Hz, 2 H; Ar*H*), 7.58 (m, 1 H; Ar*H*), 7.47 (t, *J* = 7.9 Hz; 2 H; Ar*H*), 5.82 (m, 1H; C*H*=CH_2), 5.11 (dd, *J* = 17.1, 1.5 Hz, 1 H; CH=CH_2), 5.04 (dd, *J* = 10.2, 1.3 Hz, 1 H; CH=CH_2), 4.39 (t, *J* = 7.2 Hz, 1 H; C*H*), 4.14 (m, 2 H ; OCH_2), 2.75 (m, 2 H; CH_2CH), 1.16 (t, *J* = 7.1 Hz, 3 H; CH_3);

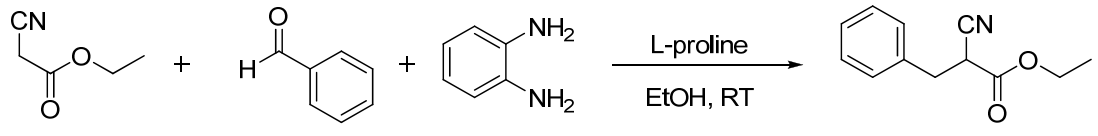
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 169.4, 136.2, 134.5, 133.5, 128.7, 128.6, 117.4, 61.4, 53.9, 33.0, 14.0;

IR 3080 (w), 2983 (w), 2938 (w), 2924 (w), 2870 (w), 2362 (w), 2329 (w), 1736 (s), 1687 (s), 1644 (w), 1597 (w), 1581 (w), 1449 (m), 1370 (w), 1325 (w), 1271 (m), 1236 (s), 1183 (m), 1116 (w), 1113 (w), 1030 (w), 1002 (w), 921 (m), 856 (w), 782 (w), 737 (w), 690 (s), 642 (m).

Characterization data of **8f** corresponded to the literature values.[11]

[11] T. Mitsudome, K. Nose, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, *Angew. Chem.-Int. Edit.* **2007**, *46*, 3288.

Ethyl 2-cyano-3-phenylpropanoate (10a)



37 **38** **39** **10a**

Following a slightly modified procedure,[12] EtOH (3.75 mL) was added to a mixture of benzaldehyde (**38**) (0.76 mL, 7.5 mmol, 2 equiv), ethyl cyanoacetate (**37**) (420 mg, 3.75 mmol, 1 equiv) and o-phenylenediamine (**39**) (405 mg, 3.75 mmol, 1 equiv). The mixture was stirred 5 min at RT and then L-proline (40 mg, 0.37 mmol, 0.1 equiv) was added. The resulting mixture was stirred at RT during 2 h. The crude product was filtered washed with dichloromethane. The resulting filtrate was concentrated and purified by flash chromatography (Hexane/EtOAc 30:1) to afford **10a** (570 mg, 2.80 mmol, 75%) as yellow oil.

R_f 0.52 (PET/EtOAc 4:1, UV/Anisaldehyde);

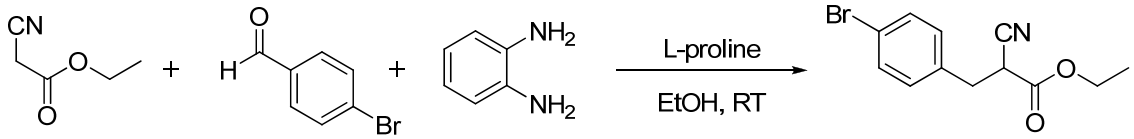
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H; Ar*H*), 4.24 (q, *J* = 7.0 Hz, 2 H; OCH_2), 3.72 (dd, *J* = 8.4, 5.8 Hz, 1 H; C*H*), 3.28 (dd, *J* = 13.8, 5.8 Hz, 1 H; CH_2Ph), 3.20 (dd, *J* = 13.8, 8.4 Hz, 1 H; CH_2Ph), 1.27 (t, *J* = 7.1 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 135.3, 128.9, 128.7, 127.7, 116.1, 62.8, 39.6, 35.7, 13.8;

IR ν 3065 (w), 3032 (w), 2986 (w), 2937 (w), 2924 (w), 2360 (w), 2339 (w), 2252 (w), 1744 (s), 1604 (w), 1498 (w), 1453 (w), 1371 (w), 1262 (m), 1206 (m), 1083 (w), 1030 (m), 914 (w), 858 (w), 749 (m), 702 (m), 636 (m).

Characterization data of **10a** corresponded to the literature values.[13]

Ethyl 3-(4-bromophenyl)-2-cyanopropanoate (10b)



37 **40** **39** **10b**

Following a slightly modified procedure,[12] EtOH (3.75 mL) was added to a mixture of 4-bromobenzaldehyde (**40**) (1.39 g, 7.50 mmol, 2 equiv), ethyl cyanoacetate (**37**) (420 mg, 3.75 mmol, 1 equiv) and o-phenylenediamine (**39**) (405 mg, 3.75 mmol, 1 equiv). The mixture was stirred 5 min at RT and then L-proline (40 mg, 0.37 mmol, 0.1 equiv) was added. The resulting mixture was stirred at RT during 4 h. The crude product was filtered and washed with dichloromethane. The resulting filtrate was concentrated and purified by flash chromatography (Hexane/EtOAc, 30:1) to afford **10b** (0.70 g, 2.5 mmol, 66%) as yellow oil.

R*f* 0.20 (PET/EtOAc 4:1, UV/Anisaldehyde);

[12] D. B. Ramachary , G. Babul Reddy, *Org. Biomol.Chem*, **2006**, *4*, 4463.
[13] D. Xue, Y. C. Chen, X. Cui, Q. W. Wang, J. Zhu, J. G. Deng, *J. Org. Chem.* **2005**, *70*, 3584.

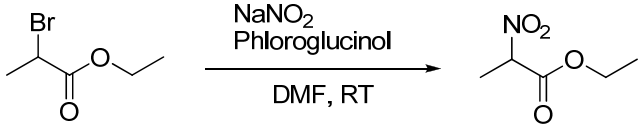
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.3 Hz, 2 H; Ar*H*), 7.16 (d, *J* = 8.3 Hz, 2H; Ar*H*), 4.24 (q, *J* = 7.1 Hz, 2 H; OCH_2), 3.70 (dd, *J* = 8.1, 5.8 Hz, 1 H; C*H*), 3.23 (dd, *J* = 13.9, 5.8 Hz, 1 H; CH_2Ph), 3.16 (dd, *J* = 13.9, 8.2 Hz, 1 H; CH_2Ph), 1.28 (t, *J* = 7.0 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 134.1, 131.8, 130.7, 121.7, 115.8, 62.9, 39.2, 34.8, 13.8.

IR ν 2985 (w), 2940 (w), 2868 (w), 2361 (w), 2338 (w), 2253 (w), 2144 (w), 1747 (s), 1594 (w), 1490 (m), 1448 (w), 1408 (w), 1371 (w), 1339 (w), 1265 (m), 1210 (m), 1163 (w), 1105 (w), 1074 (w), 1032 (w), 1016 (w), 856 (w), 834 (w), 806 (w), 738 (w), 637 (s), 617 (m).

Characterization data of **10b** corresponded to the literature values.[12]

Ethyl 2-nitropropanoate (12a)



41 **12a**

Following the reported procedure,[14] ethyl 2-bromopropanoate (**41**) (4.8 mL, 36 mmol, 1 equiv) was added to a stirred mixture of sodium nitrite (4.72 g, 68.4 mmol, 1.9 equiv) and phloroglucinol (5.00 g, 39.6 mmol, 1.1 equiv) in DMF (54 mL). The reaction mixture was stirred at RT for 3.5 h. The resulting brown mixture was poured into ice-water (150 mL) and ether (25 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with sat. $NaHCO_3$ solution, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (PET/AcOEt 10:1, 5:1, 1:1) to afford the compound **12a** (1.89 g, 12.8 mmol, 36%) as yellow liquid.

R_f 0.68 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (q, *J* = 7.1 Hz, 1 H; C*H*), 4.26 (q, *J* = 7.1 Hz, 2 H; OCH_2), 1.77 (d, *J* = 7.1 Hz, 3 H; CH_3), 1.28 (t, *J* = 7.1 Hz, 3 H; CH_3CH_2);

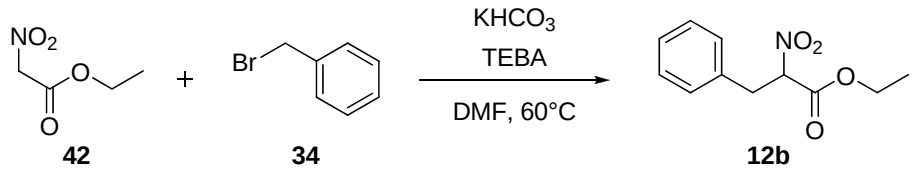
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 83.1, 62.9, 15.6, 13.8;

IR ν 2988 (w), 2947 (w), 2911 (w), 2880 (w), 2362 (w), 2338 (w), 1750 (s), 1562 (s), 1453 (m), 1391 (m), 1365 (w), 1317 (m), 1265 (w), 1205 (s), 1121 (w), 1088 (m), 1033 (m), 909 (w), 865 (m), 783 (w), 735 (w), 685 (w).

Characterization data of **12a** corresponded to the literature values.[15]

[14] H. T. Zhao, J. Joseph, H. Zhang, H. Karoui, B. Kalyanaraman, *Free Radic. Biol. Med.* **2001**, *31*, 599.
[15] V. Beraud, P. Perfetti, C. Pfister, M. Kaafarani, P. Vanelle, M. P. Crozet, *Tetrahedron* **1998**, *54*, 4923.

Ethyl 2-nitro-3-phenylpropanoate (12b)



Following the reported procedure,[16] to a stirred solution of ethyl nitroacetate (**42**) (420 µL, 3.75 mmol, 1 equiv) in DMF (4 mL) containing benzyl triethylammonium chloride (TEBA, 3.4 mg, 0.015 mmol, 0.004 equiv) and anhydrous $KHCO_3$ (190 mg, 1.87 mmol, 0.5 equiv) was added benzyl bromide (**34**) (450 µL, 3.75 mmol, 1 equiv) at RT. The reaction mixture was stirred 16 h. DMF was removed under reduced pressure and the mixture was diluted with water and extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual yellow oil was purified by flash chromatography (Hexane/EtOAc, 30:1) to afford **12b** (234 mg, 1.05 mmol, 28%) as colorless oil.

R_f 0.64 (PET/EtOAc 4:1, UV/Anisaldehyde);

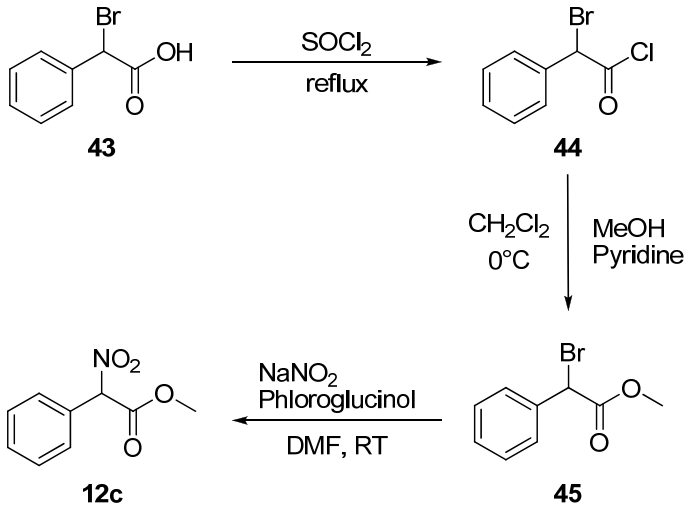
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2 H; Ar*H*), 7.22 (m, 3 H; Ar*H*), 5.33 (dd, *J* = 9.4, 5.8 Hz, 1 H; C*H*), 4.28 (qd, *J* = 7.1, 0.9 Hz, 2 H; OCH_2), 3.56 (dd, *J* = 14.6, 9.5 Hz,1 H; CH_2Ph), 3.48 (dd, *J* = 14.6, 5.9 Hz, 1 H; CH_2Ph), 1.28 (t, *J* = 7.1 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 134.1, 129.0, 128.9, 127.8, 89.2, 63.2, 36.3, 13.9;

IR ν 3090 (w), 3067 (w), 3033 (w), 2986 (w), 2934 (w), 2877 (w), 2823 (w), 2362 (m), 2338 (w), 1751 (s), 1646 (w), 1564 (s), 1497 (w), 1453 (w), 1371 (m), 1271 (m), 1211 (m), 1092 (w), 1058 (w), 1022 (m), 912 (w), 860 (w), 791 (w), 761 (w), 738 (w), 701 (m).

Characterization data of **12b** corresponded to the literature values.[17]

Methyl 2-nitro-2-phenylacetate (12c)



[16] V. N. Gogte, A. A. Natu, V. S. Pore, *Synth. Commun.* **1987**, *17*, 1421.
[17] D. B. Ramachary, M. Kishor, Y. V. Reddy, *Eur. J. Org. Chem.* **2008**, 975.

Following the reported procedure,[18] a solution of α-bromophenylacetic acid (**43**) (10.0 g, 46.5 mmol, 1 equiv) in thionyl chloride (20 mL) was refluxed for 2 h at 85 °C. The evolving gas was absorbed into a 10% sodium carbonate solution. The mixture was cooled to RT and the excess thionyl chloride was removed under reduced pressure (70 mmHg, 40 °C). The remaining part was removed after addition of heptanes in a rotary evaporator to give α-bromophenylacetyl chloride (**44**) (10.6 g, 45.3 mmol, 98%). The yellow crude product was used without purification.

α-Bromophenylacetyl chloride (**44**) (3.00 g, 13.0 mmol, 1 equiv) was slowly added via cannula to a solution of methanol (0.750 mL, 18.0 mmol, 1.43 equiv) and pyridine (1.05 mL, 13.0 mmol, 1 equiv) in CH_2Cl_2 (40 mL) at 0 °C (ice-bath). The reaction mixture was stirred for 1.5 h at 0 °C and then washed with water (40 mL), sulfuric acid (10% solution, 50 mL) and sat. $NaHCO_3$ (40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give methyl 2-bromo-2-phenylacetate (**45**) (2.62 g, 11.4 mmol, 88%) as yellow oil. The crude product was used without purification.

To a stirred solution of sodium nitrite (1.34 g, 19.4 mmol, 1.7 equiv) and phloroglucinol (1.29 g, 10.2 mmol, 0.9 equiv) in *N*,*N*-dimethylformamide (23 mL) was added methyl α-bromophenylacetate (**45**) (2.60 g, 11.4 mmol, 1 equiv) at RT. The reaction mixture was stirred 12 h, then poured in ice water (100 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3/Na_2CO_3$, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (CH_2Cl_2/EtOAc, 40:1) to afford compound **12c** (1.04 g, 5.33 mmol, 47%) as yellow oil.

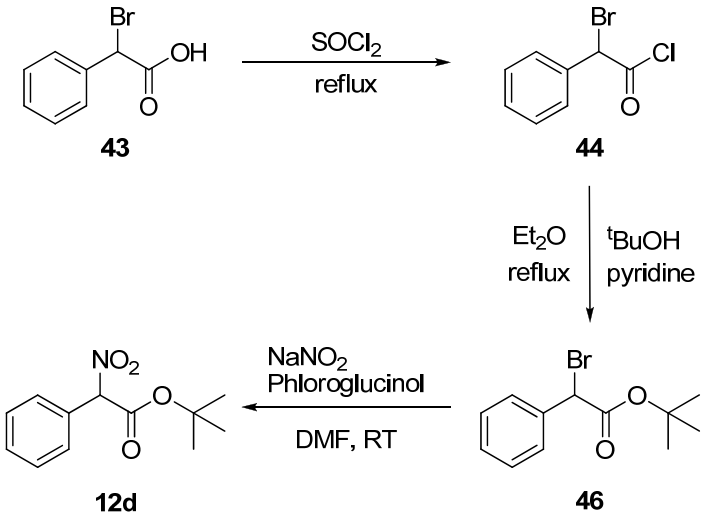
R_f 0.5 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 5 H; Ar*H*), 6.20 (s, 1 H; C*H*), 3.90 (s, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 130.5, 129.8, 129.3, 129.0, 91.5, 54.9.

Characterization data of **12c** corresponded to the literature values.[19]

***tert*-Butyl 2-nitro-2-phenylacetate (12d)**



[18] K. Stolze, N. Rohr-Udilova, T. Rosenau, A. Hofinger, D. Kolarich, H. Nohl, *Bioorg. Med. Chem.* **2006**, *14*, 3368.
[19] M. Hugener, H. Heimgartner, *Helv. Chim. Acta* **1995**, *78*, 1490.

Following the reported procedures,[18,20] a solution of α-bromophenylacetic acid (**43**) (10.0 g, 46.5 mmol, 1 equiv) in thionyl chloride (20 mL) was refluxed for 2 h at 85 °C. The evolving gas was absorbed into a 10% sodium carbonate solution. The mixture was cooled at RT and the excess of thionyl chloride was removed under reduced pressure (70 mmHg, 40 °C). The remaining part was removed after addition of heptanes in a rotary evaporator to give α-bromophenylacetyl chloride (**44**) (10.6 g, 45.3 mmol, 98%). The yellow crude product was used without purification.

α-Bromophenylacetyl chloride (**44**) (3.00 g, 13.0 mmol, 1 equiv) was slowly added by cannula to a solution of *tert*-butyl alcohol (1.80 mL, 18.0 mmol, 1.43 equiv) and pyridine (1.0 mL, 13 mmol, 1 equiv) in Et_2O (40 mL). The reaction mixture was stirred for 2 h at reflux (40 °C). The cooled mixture was washed with an equal volume of water, sulfuric acid (10% solution, 50 mL) and sat. $NaHCO_3$ (40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **46** as yellow oil (2.45 g, 9.04 mmol, 70%). The crude product was used without purification.

To a stirred solution of sodium nitrite (1.04 g, 15.0 mmol, 1.7 equiv) and phloroglucinol (1.00 g, 7.96 mmol, 0.9 equiv) in *N*,*N*-dimethylformamide (18 mL) was added *tert*-butyl α-bromophenylacetate (**46**) (2.40 g, 8.85 mmol, 1 equiv) at RT. The reaction mixture was stirred 16 h, then poured in ice water (100 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with sat. $NaHCO_3$/Na_2CO_3, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (CH_2Cl_2/EtOAc, 40:1) to afford a yellow oil. The obtained oil was dissolved in Et_2O and washed with sat. NaOH. The aqueous layer was acidified with 1 M HCl and extracted with CH_2Cl_2. The organic layer was dried with Mg_2SO_4 and concentrated to give product **12d** (940 mg, 3.96 mmol, 45%) as yellow oil.

R_f 0.43 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H; Ar*H*), 7.65 (m, 1 H; Ar*H*), 7.48 (m, 2 H; Ar*H*), 6.08 (s, 1 H; C*H*), 1.50 (s, 3 H; OC(CH_3)$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 130.5, 129.8, 129.3, 129.0, 91.5, 85.0, 27.7.

HRMS(ESI) calcd for $C_{12}H_{14}O_4^-$ (M-H) 236.0923, found 236.0928.

3. Alkynylation Reactions

3.1 Catalytic alkynylation using TBAF

General procedure 1: A solution of substrate (1.0 equiv) and alkynyl benziodoxolone reagent (1.3 equiv) in dried THF (60 mM) was stirred at -78 °C for 5 min under nitrogen. After this period of time, TBAF (1 M, 1.3 equiv) was added and mixture was vigorously stirred at -78 °C. The reaction was monitored by TLC analysis (PET/EtOAc, 4:1, UV and *p*-anisaldehyde) and was complete at -78 °C in the indicated time, or was slowly let to warm up to 10 °C during the indicated time. The reaction mixture was quenched with deactivated silica gel and the solvent was evaporated under reduced pressure. The product was purified via flash chromatography (SiO_2, Hexane/EtOAc) with the indicated solvent ratio.

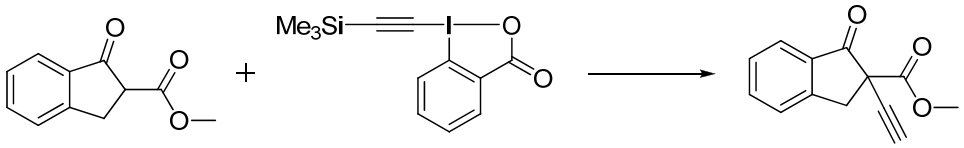
[20] a) M. S. Newman, J. A. Cella, *J. Org. Chem.* **1974**, *39*, 214. b) N. Kornblum, R. K. Blackwood, J. W. Powers, *J. Am. Chem. Soc.* **1957**, *79*, 2507.

General procedure 2: A solution of alkynyl benziodoxolone reagent (1.3 equiv) in THF/CH_2Cl_2 (5:1) was added via syringe pump to a mixture of the corresponding nucleophile (1.0 equiv) and TBAF (1 M, 1.3 equiv) in dried THF (60 mM) at -78 °C to 10 °C for 18-20 h. The reaction was monitored by TLC analysis (PET/EtOAc 4:1, UV and *p*-anisaldehyde). The reaction was quenched with deactivated silica gel and the solvent was evaporated under reduced pressure. The product was purified via flash chromatography (SiO_2, Hexane/EtOAc) with the indicated solvent ratio.

3.2 Catalytic phase-transfer alkynylation

General procedure 3: A solution of saturated base solution (0.2 M) was added to a solution of phase-transfer catalyst (10% mol) and alkynyl benziodoxolone reagent (1.3 equiv) in dry toluene (50 mM). The mixture was stirred at 0 °C for 5 min under nitrogen. After this period of time, the substrate (1.0 equiv) was added and the biphasic mixture was vigorously stirred at 0 °C. The reaction was monitored by TLC analysis (PET/EtOAc 4:1, UV and *p*-anisaldehyde). After the indicated time, the reaction mixture was quenched with water and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were recollected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography (SiO_2, Hexane/EtOAc) with the indicated solvent ratio.

Methyl 2-ethynyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (5a)



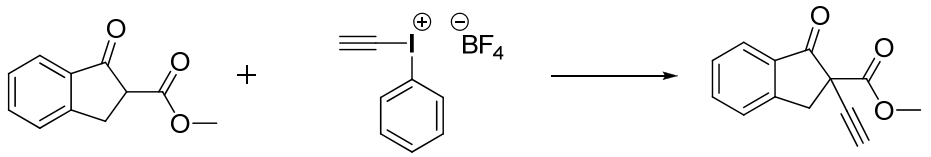
4a **2** **5a**

Alkynylation using TBAF:

Following general procedure **1**, on a 0.40 mmol scale using **4a** (76 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was was quenched after 1.5 h at -78 °C. Purification by flash chromatography (Hexane/EtOAc 10:1) afforded **5a** (83 mg, 0.39 mmol, 98 %) as yellow solid.

Phase-transfer alkynylation:

Following general procedure **3**, on a 0.30 mmol scale using **4a** (57 mg, 0.30 mmol, 1.0 equiv), TMS reagent **2** (134 mg, 0.390 mmol, 1.3 equiv), sat. KF solution 33% w/w (1.5 mL) and tetramethyl ammonium chloride as phase-transfer catalyst (3.3 mg, 0.030 mmol, 0.1 equiv). The reaction was finished after 20 h at 0 °C. Purification by flash chromatography (Hexane/EtOAc 20:1) afforded **5a** (56 mg, 0.26 mmol, 87 %) as a yellow solid.



4a **47** **5a**

Alkynylation using alkynyliodonium salt:

Following the reported procedure,[21] a solution of **4a** (76 mg, 0.40 mmol, 1 equiv) and NaH (11 mg, 0.48 mmol, 1.2 equiv) in THF (2 mL) was stirred at RT for 1 h. Trimethylsilylethynyl(phenyl)iodonium tetrafluoroborate (**47**) (150 mg, 0.480 mmol, 1.2 equiv) was then added and the resulting mixture was stirred at RT for 3 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (Hexane/EtOAc, 20:1) to afford compound **5a** (59 mg, 0.27 mmol, 69%) as yellow solid.

R_f 0.33 (PET/EtOAc 4:1, UV/Anisaldehyde);

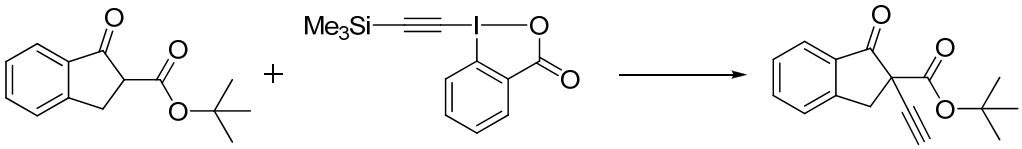
Mp 96-98 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 1 H; Ar*H*), 7.67 (t, *J* = 7.5 Hz, 1 H; Ar*H*), 7.49 (d, *J* = 7.7 Hz, 1H; Ar*H*), 7.43 (t, *J* = 7.5 Hz, 1 H; Ar*H*), 3.94 (d, *J* = 17.1 Hz, 1 H; C*H*$_2$), 3.80 (s, 3H; C*H*$_3$), 3.52 (d, *J* = 17.1 Hz, 1 H; C*H*$_2$), 2.42 (s, 1 H; C≡C*H*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 167.9, 151.9, 135.9, 132.7, 128.0, 126.2, 125.4, 79.6, 72.2, 54.9, 53.5, 40.2;IR ν 3283 (w), 2976 (w), 2937 (w), 2877 (w), 1730 (s), 1608 (w), 1462 (w), 1436 (w), 1368 (w), 1262 (w), 1214 (w), 1152 (m), 1066 (w), 958 (w), 913 (w), 847 (w), 802 (w), 740 (w), 687 (w), 639 (w);

HRMS(ESI) calcd for $C_{13}H_{10}O_3Na^+$ (M+Na) 237.0528, found 237.0524.

***tert*-Butyl 2-ethynyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (5b)**



4b **2** **5b**

Alkynylation using TBAF:

Following general procedure **1**, on a 0.40 mmol scale using **4b** (93 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was finished after 3 h at -78 °C. Purification by flash chromatography (Hexane/EtOAc 20:1) afforded **5b** (95.8 mg, 0.374 mmol, 94 %) as colorless solid.

Phase-transfer alkynylation;

Following general procedure **3**, on a 0.30 mmol scale using **4b** (69 mg, 0.30 mmol, 1.0 equiv), TMS reagent **2** (134 mg, 0.390 mmol, 1.3 equiv), sat. KF solution 33% w/w (1.5 mL) and tetramethyl ammonium chloride as phase-transfer catalyst (3.3 mg, 0.03 mmol, 0.1 equiv). The reaction was finished after 24 h at 0 °C. Purification by flash chromatography (Hexane/EtOAc 20:1) afforded **5b** (54 mg, 0.21 mmol, 70 %) as a colorless solid.

Following general procedure **3**, on a 0.30 mmol scale using **4b** (69 mg, 0.30 mmol, 1.0 equiv), TMS reagent **2** (134 mg, 0.390 mmol, 1.3 equiv), sat. KF solution 33% w/w (1.5 mL) and cinchonidine-derived catalyst **21** (21 mg, 0.030 mmol, 0.1 equiv). The reaction was finished after 2 h at 0 °C. The crude product

[21] Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Chem. Soc. Chem. Commun.* **1990**, 118.

was purified via silica gel flash chromatography (Hexane/EtOAc 15:1) to afford **5b** (28.6 mg, 0.110 mmol, 37%) as a white solid. HPLC analysis in Chiralpack IC column gave 40% *ee* for **5b**.

R_f 0.74 (PET/EtOAc 4:1, UV/Anisaldehyde);

Mp 94-97 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 1 H; Ar*H*), 7.65 (t, *J* = 7.5 Hz, 1 H; Ar*H*), 7.49 (d, *J* = 7.7 Hz, 1H; Ar*H*), 7.43 (t, *J* = 7.5 Hz, 1 H; Ar*H*), 3.84 (d, *J* = 17.1 Hz, 1 H; CH_2), 3.50 (d, *J* = 17.1 Hz, 1 H; CH_2), 2.39 (s, 1 H; C≡C*H*), 1.43 (s, 9 H; OC(CH_3)$_3$);

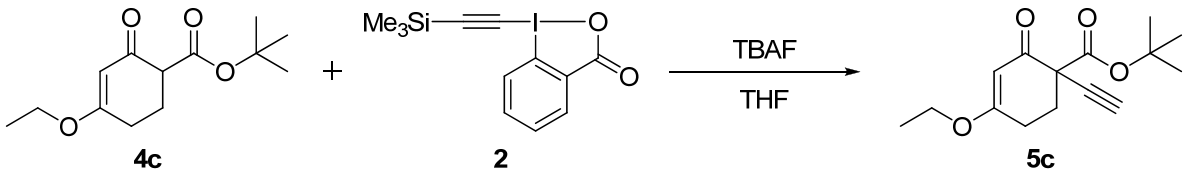
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 166.6, 152.2, 135.7, 133.5, 128.1, 126.3, 125.6, 83.5, 80.3, 72.1, 56.2, 40.6, 27.6;

IR ν 3308 (w), 2981 (w), 2942 (w), 2866 (w), 2362 (w), 2255 (w), 1723 (m), 1609 (w), 1466 (w), 1372 (w), 1287 (w), 1256 (w), 1153 (w), 907 (s), 806 (w), 733 (s), 651 (m);

HRMS(ESI) calcd for $C_{16}H_{16}O_3Na^+$ (M+Na) 279.0997, found 279.1006;

HPLC analysis: Daicel Chiralpack IC column; 20 °C; 0 to 32 min: 1 mL/min; solvent system: ^{i}PrOH/hexanes, 0 to 5 min 5/95, 5 to 25 min 5/95 to 30/70, 25 min to 27 min 30/70 to 5/95, 27 min to 32 min 5/95; minor peak: 16.9 min, major peak 18.8 min.

***tert*-Butyl 4-ethoxy-1-ethynyl-2-oxocyclohex-3-enecarboxylate (5c)**



4c **2** **5c**

The reaction was carried out following general procedure **2** on a 0.40 mmol scale using **4c** (96 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 18 h. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 20:1) afforded **5c** (53 mg, 0.20 mmol, 50%) as a colorless solid.

R_f 0.61 (PET/EtOAc 4:1, UV/Anisaldehyde);

Mp 106-109 °C;

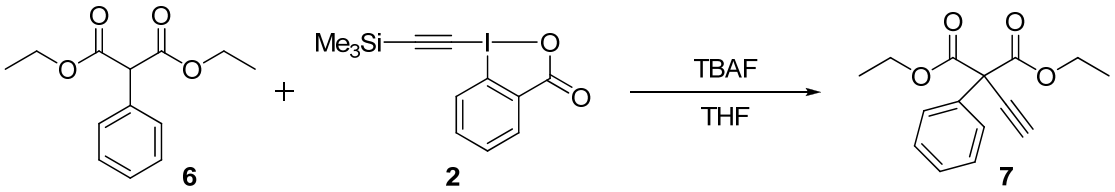
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1 H; C=CC*H*), 3.91 (q, *J* = 7.0 Hz, 2 H; OCH_2), 2.58 (m, 2 H; CH_2), 2.40 (s, 1 H; C≡C*H*), 2.19 (dt, *J* = 12.8, 5.0 Hz, 2H; CH_2), 1.47 (s, 9 H; OC(CH_3)$_3$), 1.36 (t, *J* = 7.0 Hz, 3H; OCH_2CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 177.0, 167.4, 100.3, 82.9, 79.3, 73.5, 64.6, 54.5, 31.0, 27.7, 26.2, 14.0;

IR ν 3266 (w), 2982 (w), 2940 (w), 2907 (w), 2359 (w), 2311 (w), 2255 (w), 2118 (w), 1733 (m), 1667 (s), 1602 (s), 1478 (w), 1453 (w), 1378 (m), 1314 (w), 1252 (s), 1193 (s), 1155 (s), 1095 (w), 1022 (m), 915 (w), 890 (w), 841 (m), 822 (w), 799 (w), 736 (m), 671 (m), 653 (m), 644 (w);

HRMS (ESI) calcd for $C_{15}H_{21}O_4^+$ (M+H) 265.1440, found 265.1449.

Diethyl 2-ethynyl-2-phenylmalonate (7)



The reaction was carried out following general procedure **1** on a 0.40 mmol scale using diethyl 2-phenylmalonate (**6**) (86 µL, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (248 mg, 0.720 mmol, 1.8 equiv). The reaction was stirred at -78 °C during 5 h and warm up to 10 °C over 15 h before quenching. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 20:1) afforded **7** (98 mg, 0.38 mmol, 95%) as colorless oil.

R_f 0.22 (PET/EtOAc 4:1, UV/Anisaldehyde);

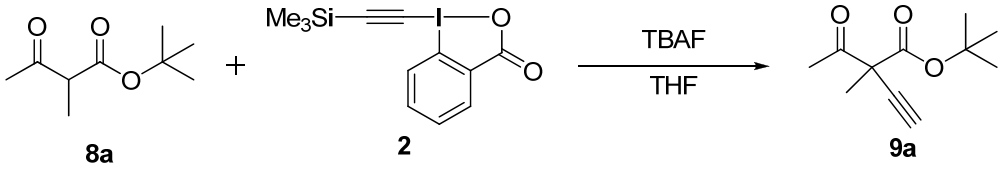
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 2 H; Ar*H*), 7.37 (m, 3 H; Ar*H*), 4.29 (q, *J* = 7.1 Hz, 4 H; OCH_2), 2.78 (s, 1 H; C≡C*H*), 1.28 (t, *J* = 7.1 Hz, 6 H; OCH_2CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 133.9, 128.6, 128.3, 128.1, 80.1, 78.3, 76.4, 63.0, 13.8;

IR ν 3282 (w), 3063 (w), 2985 (w), 2936 (w), 2362 (w), 2338 (w), 1741 (s), 1600 (w), 1494 (w), 1450 (w), 1391 (w), 1368 (w), 1297 (w), 1247 (s), 1222 (s), 1099 (w), 1094 (w), 1038 (m), 954 (w), 864 (w), 735 (m), 698 (m), 669 (m), 636 (m);

HRMS (ESI) calcd for $C_{15}H_{17}O_4^+$ (M+H) 261.1127, found 261.1125.

***tert*-Butyl 2-acetyl-2-methylbut-3-ynoate (9a)**



The reaction was carried out following general procedure **1** from **8a** (69 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was stirred at -78 °C during 5 h and warm up to 10 °C over 12 h before quenching. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc, 10:1) afforded **9a** (70 mg, 0.36 mmol, 90%) as colorless oil.

R_f 0.69 (PET/EtOAc 4:1, UV/Anisaldehyde);

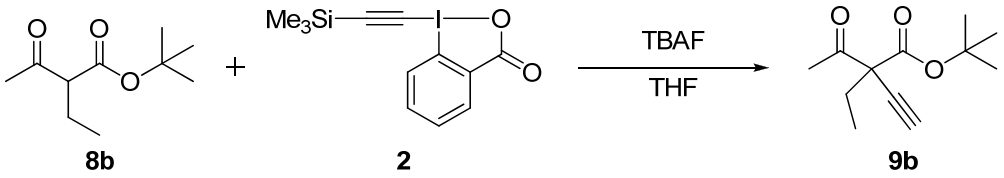
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 1 H; C≡C*H*), 2.36 (s, 3 H; COCH_3), 1.54 (s, 3 H; CH_3), 1.45 (s, 9 H; $OC(CH_3)_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 167.6, 83.2, 81.3, 74.1, 56.2, 27.6, 26.2, 21.4;

IR ν 3729 (w), 3705 (w), 3681 (w), 3626 (w), 3598 (w), 3276 (w), 2981 (w), 2938 (w), 2876 (w), 2358 (w), 2293 (w), 1729 (s), 1559 (w), 1456 (w), 1376 (w), 1258 (m), 1158 (s), 1118 (w), 1020 (w), 915 (w), 842 (w), 796 (w), 740 (w), 678 (w), 652 (w);

Analysis Calcd for $C_{11}H_{16}O_3$: C 67.32, H 8.22; found: C 67.04, H 8.51.

***tert*-Butyl 2-acetyl-2-ethylbut-3-ynoate (9b)**



The reaction was carried out following general procedure **2** from **8b** (75 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 20 h. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc, 20:1) afforded **9b** (52 mg, 0.25 mmol, 63%) as yellow oil.

R_f 0.66 (PET/EtOAc 4:1, UV/Anisaldehyde);

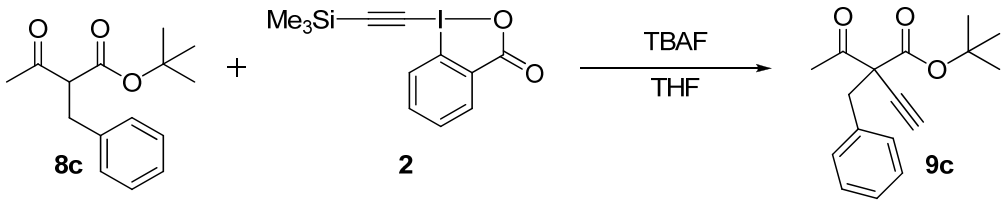
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 1 H; C≡C*H*), 2.34 (s, 3 H; COCH_3), 1.99 (m, 2 H; CH_2), 1.45 (s, 9 H; OC(CH_3)$_3$), 0.99 (t, *J* = 7.4 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 167.0, 83.1, 79.9, 75.2, 62.2, 27.9, 27.7, 26.8, 9.2;

IR ν 3288 (w), 2980 (m), 2936 (w), 2883 (w), 2364 (w), 2333 (w), 1725 (s), 1566 (w), 1460 (w), 1370 (m), 1250 (s), 1151 (s), 1034 (w), 946 (w), 842 (m), 739 (w), 665 (w), 636 (m);

HRMS (ESI) calcd for $C_{12}H_{18}O_3Na^+$ (M+Na) 233.1154, found 233.1147.

***tert*-Butyl 2-acetyl-2-benzylbut-3-ynoate (9c)**



The reaction was carried out following general procedure **1** from **8c** (129 mg, 0.520 mmol, 1.00 equiv) and TMS reagent **2** (230 mg, 0.670 mmol, 1.3 equiv). The reaction was stirred at -78 °C during 5 h and warm up to 10 °C over 15 h before quenching. Purification by flash chromatography (Hexane/EtOAc, 10:1) afforded **9c** (109 mg, 0.400 mmol, 77%) as yellow oil.

R_f 0.46 (PET/EtOAc 4:1, UV/Anisaldehyde);

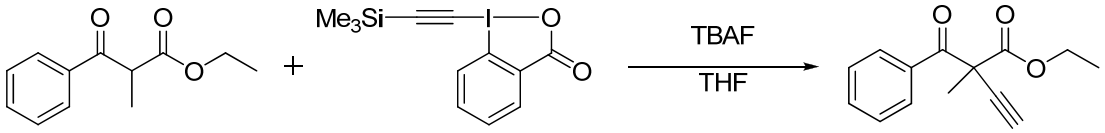
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5 H; Ar*H*), 3.31 (s, 2 H; CH_2), 2.59 (s, 1 H; C≡C*H*), 2.30 (s, 3 H; CH_3), 1.44 (s, 9 H; OC(CH_3)$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 166.4, 135.7, 130.4, 128.0, 127.1, 83.4, 80.2, 76.8, 62.3, 40.0, 27.6, 27.4;

IR ν 3282 (w), 3065 (w), 3033 (w), 2981 (w), 2935 (w), 2359 (w), 2342 (w), 1745 (s), 1727 (s), 1605 (w), 1498 (w), 1456 (w), 1395 (w), 1371 (m), 1253 (m), 1148 (s), 1083 (w), 1034 (w), 981 (w), 914 (w), 842 (m), 768 (w), 738 (m), 701 (s);

HRMS (ESI) calcd for $C_{17}H_{20}O_3Na^+$ (M+Na) 295.1310, found 295.1303.

Ethyl 2-benzoyl-2-methylbut-3-ynoate (9d)



8d **2** **9d**

The reaction was carried out following general procedure **1** from **8d** (82 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was stirred at -78 °C during 5 h and warm up to 10 °C over 7 h before quenching. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 10:1) afforded **9d** (76 mg, 0.33 mmol, 83%) as yellow oil.

R_f 0.35 (PET/EtOAc 4:1, UV/Anisaldehyde);

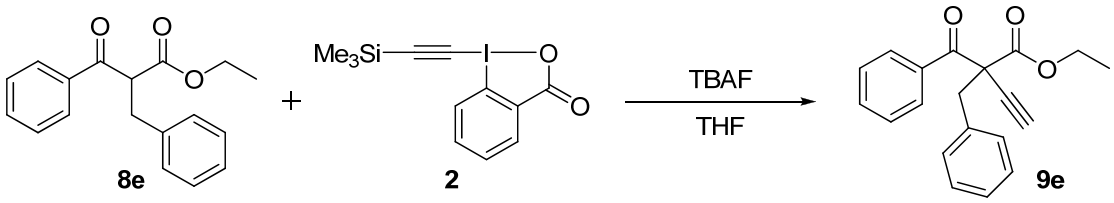
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 2 H; Ar*H*), 7.54 (m, 1 H; Ar*H*), 7.42 (m, 2 H; Ar*H*), 4.15 (qd, *J* = 7.1, 1.5 Hz, 2 H; CH_2), 2.64 (s, 1 H; C≡C*H*), 1.81 (s, 3 H; CH_3), 1.07 (t, *J* = 7.1 Hz, 3 H; OCH$_2$CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 170.1, 134.1, 133.3, 129.4, 128.3, 81.1, 76.8, 62.4, 52.6, 23.5, 13.6;

IR ν 3286 (w), 3065 (w), 2992 (w), 2943 (w), 2880 (w), 2841 (w), 2361 (w), 1742 (m), 1699 (s), 1597 (w), 1476 (w), 1450 (m), 1374 (w), 1299 (w), 1258 (s), 1229 (s), 1167 (m), 1121 (m), 1091 (m), 1022 (m), 971 (m), 861 (w), 792 (m), 744 (w), 697 (m), 641 (w);

HRMS (ESI) calcd for $C_{14}H_{15}O_3^+$ (M+H) 231.1021, found 231.1017.

Ethyl 2-benzoyl-2-benzylbut-3-ynoate (9e)



8e **2** **9e**

The reaction was carried out following general procedure **2** from **8e** (113 mg, 0.400 mmol, 1.00 equiv) and TMS reagent **2** (248 mg, 0.720 mmol, 1.8 equiv). The reaction was quenched after 20 h. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 20:1) afforded **9e** (114 mg, 0.372 mmol, 93%) as yellow oil.

R_f 0.6 (PET/EtOAc 4:1, UV/Anisaldehyde);

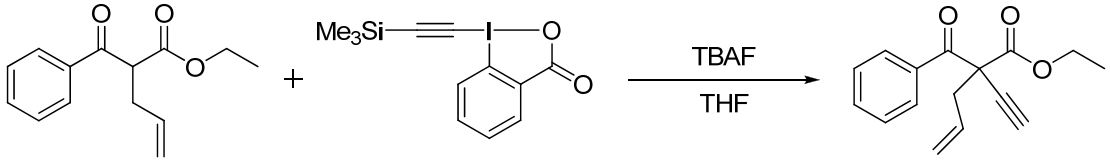
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m, 2 H; Ar*H*), 7.57 (m, 4 H; Ar*H*), 7.45 (t, *J* = 7.8 Hz, 2 H; Ar*H*), 7.32 (d, *J* = 3.1 Hz, 2 H; Ar*H*), 4.07 (q, *J* = 7.1 Hz, 2 H; OCH_2), 3.57 (d, *J* = 13.6 Hz, 1 H; CH_2Ph), 3.51 (d, *J* = 13.4 Hz, 1 H; CH_2Ph), 2.73 (s, 1 H; C≡C*H*), 1.03 (t, *J* = 7.1 Hz, 3H; OCH_2CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 168.5, 135.3, 134.5, 133.3, 130.4, 129.4, 128.3, 128.0, 127.2, 79.9, 79.2, 62.3, 59.0, 41.9, 13.6;

IR ν 3288 (w), 3065 (w), 3032 (w), 2981 (w), 2939 (w), 2907 (w), 2362 (w), 2339 (w), 1730 (s), 1696 (s), 1603 (w), 1599 (w), 1496 (w), 1450 (m), 1392 (w), 1369 (w), 1310 (w), 1263 (s), 1228 (s), 1187 (s), 1100 (m), 1045 (m), 1023 (m), 912 (w), 857 (w), 798 (w), 793 (w), 738 (m), 698 (s), 665 (s), 600 (w);

HRMS (ESI) calcd for $C_{20}H_{19}O_3^+$ (M+H) 307.1334, found 307.1339.

Ethyl 2-benzoyl-2-ethynylpent-4-enoate (9f)



8f **2** **9f**

The reaction was carried out following general procedure **2** from **8f** (93 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 20 h. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 20:1) afforded **9f** (90 mg, 0.35 mmol, 88%) as yellow oil.

R_f 0.26 (PET/EtOAc 4:1, UV/Anisaldehyde);

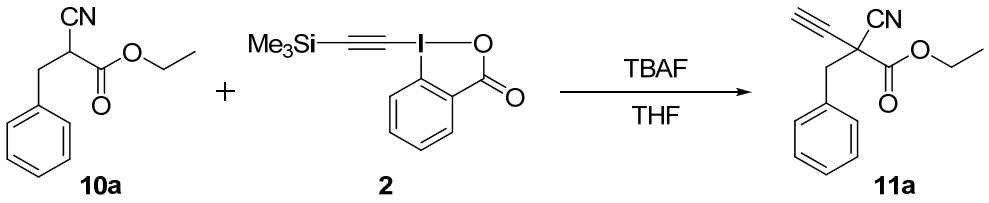
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.1 Hz, 2 H; Ar*H*), 7.55 (t, *J* = 7.4 Hz, 1 H; Ar*H*), 7.43 (t, *J* = 7.8 Hz, 2 H; Ar*H*), 5.96 (m, 1 H; H_2C=C*H*), 5.19 (m, 2 H; H_2C=CH), 4.13 (qd, *J* = 7.1, 2.6 Hz, 2 H; OCH_2), 3.01 (dd, *J* = 13.9, 6.2 Hz, 1 H; CH_2), 2.92 (dd, *J* = 13.8, 8.3 Hz, 1 H; CH_2), 2.69 (s, 1 H; C≡C*H*), 1.08 (t, *J* = 7.1 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 168.8, 134.3, 133.4, 132.1, 129.4, 128.4, 119.3, 79.7, 78.2, 62.5, 57.6, 40.9, 13.9;

IR ν 3287 (w), 3074 (w), 2983 (w), 2934 (w), 2361 (w), 2338 (w), 1735 (s), 1696 (s), 1644 (w), 1598 (w), 1582 (w), 1449 (m), 1368 (w), 1297 (m), 1274 (m), 1233 (s), 1212 (s), 1152 (m), 1096 (w), 1040 (w), 1024 (w), 1002 (w), 924 (m), 854 (w), 792 (w), 741 (w), 695 (s), 655 (s);

HRMS (ESI) calcd for $C_{16}H_{17}O_3^+$ (M+H) 257.1178, found 257.1178.

Ethyl 2-benzyl-2-cyanobut-3-ynoate (11a)



The reaction was carried out following general procedure **1** from **10a** (80 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 4 h at -78 °C. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 10:1) afforded **11a** (81 mg, 0.36 mmol, 90%) as orange oil.

R_f 0.52 (PET/EtOAc 4:1, UV/Anisaldehyde);

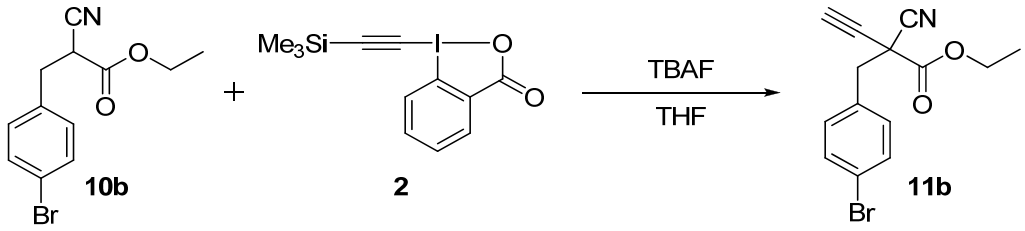
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5 H; Ar*H*), 4.28 (q, *J* = 7.2 Hz, 2 H; OCH_2), 3.45 (d, *J* = 13.4 Hz, 1 H; CH_2Ph), 3.39 (d, *J* = 13.4 Hz, 1 H; CH_2Ph), 2.62 (s, 1 H; C≡C*H*), 1.27 (t, *J* = 7.2 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 132.6, 130.3, 128.5, 128.4, 115.1, 75.8, 75.0, 64.1, 44.3, 44.0, 13.8;

IR ν 3287 (w), 3066 (w), 3035 (w), 2987 (w), 2940 (w), 2907 (w), 2874 (w), 2362 (w), 2338 (w), 2253 (w), 2130 (w), 1752 (s), 1606 (w), 1588 (w), 1498 (w), 1452 (w), 1393 (w), 1370 (w), 1298 (w), 1232 (s), 1100 (w), 1034 (w), 914 (w), 856 (w), 773 (w), 739 (w), 701 (s), 668 (m), 626 (w);

HRMS (ESI) calcd for $C_{14}H_{14}NO_2^+$ (M+H) 228.1024, found 228.1034.

Ethyl 2-(4-bromobenzyl)-2-cyanobut-3-ynoate (11b)



The reaction was carried out following general procedure **1** from **10b** (120 mg, 0.400 mmol, 1.00 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 1.5 h at -78 °C. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 10:1) afforded **11b** (91mg, 0.30 mmol, 75%) as yellow oil.

R_f 0.46 (PET/EtOAc 4:1, UV/Anisaldehyde);

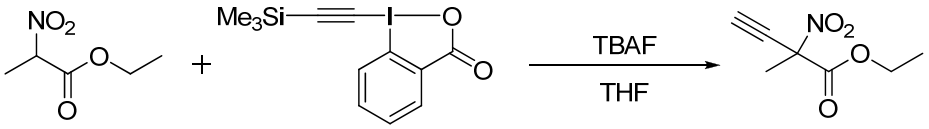
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.48 (d, *J* = 8.5 Hz, 2 H; Ar*H*), 7.23 (d, *J* = 8.5 Hz, 2 H; Ar*H*), 4.30 (q, *J* = 7.2 Hz, 2 H; OCH_2), 3.39 (d, *J* = 13.5 Hz, 1 H; CH_2Ph), 3.33 (d, *J* = 13.5 Hz, 1 H; CH_2Ph), 2.62 (s, 1 H; C≡C*H*), 1.30 (t, *J* = 7.1 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 131.6, 131.1, 130.1, 122.1, 114.5, 80.6, 75.7, 64.0, 42.7, 36.2, 13.2;

IR 3291 (w), 2986 (w), 2940 (w), 2907 (w), 2871 (w), 2360 (w), 2333 (w), 2251 (w), 2221 (w), 2126 (w), 1966 (w), 1906 (w), 1752 (s), 1595 (w), 1489 (m), 1445 (w), 1408 (w), 1369 (w), 1288 (w), 1233 (s), 1115 (m), 1073 (m), 1013 (s), 955 (w), 855 (m), 823 (m), 801 (w), 801 (w), 773 (w), 726 (w), 663 (m);

Analysis Calcd for $C_{14}H_{12}BrNO_2$: C 54.92, H 3.95, N 4.57; found: C 55.14, H 4.15, N 4.48.

Ethyl 2-methyl-2-nitrobut-3-ynoate (13a)



12a **2** **13a**

The reaction was carried out following general procedure **1** from **12a** (59 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 3 h at -78 °C. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc, 10:1) afforded **13a** (52 mg, 0.30 mmol, 75%) as yellow oil.

R_f 0.54 (PET/EtOAc 4:1, UV/Anisaldehyde);

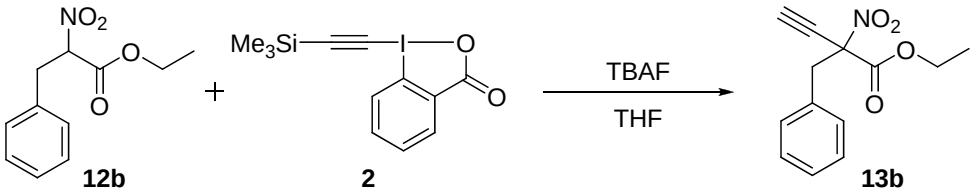
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (m, 2 H; OC*H*$_2$), 2.94 (s, 1 H; C≡C*H*), 2.08 (s, 3 H; C*H*$_3$), 1.33 (t, *J* = 7.1 Hz, 3 H; OCH$_2$C*H*$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 86.3, 79.6, 75.7, 64.1, 24.9, 13.7;

IR ν 3289 (w), 2987 (w), 2943 (w), 2910 (w), 2361 (m), 2338 (w), 2129 (w), 1759 (s), 1570 (s), 1445 (w), 1384 (w), 1344 (w), 1255 (s), 1196 (m), 1131 (m), 1014 (w), 913 (w), 852 (w), 776 (w), 736 (w), 686 (m);

Analysis Calcd for $C_7H_9NO_4$: C 49.12, H 5.30, N 8.18; found: C 49.16, H 5.22, N 8.52.

Ethyl 2-benzyl-2-nitrobut-3-ynoate (13b)

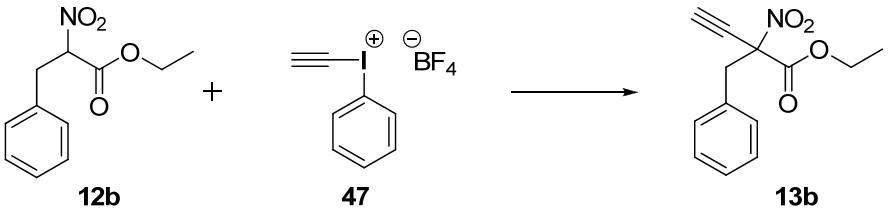


12b **2** **13b**

Alkynylation using TBAF:

The reaction was carried out following general procedure **1** from **12b** (89 mg, 0.40 mmol, 1.0 equiv) with TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 1 h at -78 °C. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 8:1) afforded **13b** (92 mg, 0.37 mmol, 93%) as yellow oil.

Following general procedure **1**, using **12b** (1.00 g, 4.66 mmol, 1.0 equiv) and TMS reagent **2** (2.00 g, 6.06 mmol, 1.3 equiv), the reaction was finished after 1.5 h at -78 °C. Purification by flash chromatography (Hexane/EtOAc 20:1) afforded **13b** (880 mg, 0.356 mmol, 77 %) as yellow oil.



Alkynylation using alkynyliodonium salt:

Following the reported procedure,[21] a solution of **12b** (89 mg, 0.40 mmol, 1 equiv) and NaH (11 mg, 0.48 mmol, 1.2 equiv) in THF (2 mL) was stirred at RT for 1 h. Trimethylsilylethynyl(phenyl)iodonium tetrafluoroborate (**47**) (150 mg, 0.480 mmol, 1.2 equiv) was then added and the resulting mixture was stirred at RT for 1.5 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (Hexane/EtOAc, 20:1) to afford compound **13b** (46.0 mg, 0.186 mmol, 46%) as yellow oil.

R_f 0.7 (PET/EtOAc 4:1, UV/Anisaldehyde);

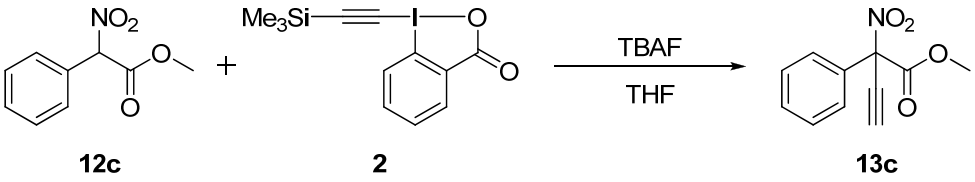
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 3 H; Ar*H*), 7.28 (m, 2 H; Ar*H*), 4.37 (m, 2 H; OCH_2), 3.81 (d, *J* = 14.1, 1 H; CH_2Ph), 3.65 (d, *J* = 14.1 Hz, 1 H; CH_2Ph), 3.03 (s, 1 H; C≡C*H*), 1.34 (t, *J* = 7.1 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 131.9, 130.3, 128.6, 128.3, 91.3, 82.6, 74.1, 64.3, 42.6, 13.7;

IR 3037 (w), 2949 (w), 2866 (w), 2361 (m), 2333 (w), 2147 (w), 1520 (w), 1462 (w), 1302 (w), 1239 (w), 1045 (w), 913 (s), 845 (w), 797 (w), 745 (s), 668 (w), 626 (w);

Analysis Calcd for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, N 5.66; found: C 63.16, H 5.31, N 5.72.

Methyl 2-nitro-2-phenylbut-3-ynoate (13c)



Alkynylation using TBAF:

The reaction was carried out following general procedure **1** from **12c** (170 mg, 0.871 mmol, 1.00 equiv) with TMS reagent **2** (389 mg, 1.13 mmol, 1.3 equiv). The reaction was quenched after 1 h at -78 °C. Purification by flash chromatography (Hexane/EtOAc, 20:1) afforded **13c** (152 mg, 0.693 mmol, 80 %) as orange oil.

Phase-transfer alkynylation:

Following general procedure **3**, on a 0.30 mmol scale using **12c** (59 mg, 0.30 mmol, 1.0 equiv), TMS reagent **2** (134 mg, 0.390 mmol, 1.3 equiv), sat. KF solution 33% w/w (1.5 mL) and tetramethyl ammonium chloride as phase-transfer catalyst (3.3 mg, 0.030 mmol, 0.1 equiv), the reaction was finished after 2 h at 0 °C. Purification by flash chromatography (Hexane/EtOAc 20:1) afforded **13c** (16 mg, 0.073 mmol, 24 %) as a orange oil.

R_f 0.45 (PET/EtOAc 4:1, UV/Anisaldehyde);

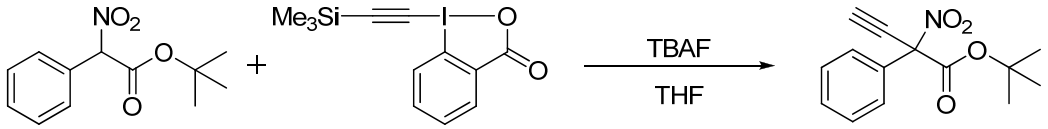
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 2 H; Ar*H*), 7.47 (m, 3 H; Ar*H*), 3.94 (s, 3 H; CH_3), 3.24 (s, 1 H; C≡C*H*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 130.9, 130.9, 128.7, 82.5, 74.6, 74.4, 54.7 (one aryl carbon was not resolved).

IR ν 3289 (w), 2958 (w), 2866 (w), 2363 (w), 2126 (w), 1756 (m), 1675 (m), 1607 (m), 1573 (s), 1497 (w), 1455 (m), 1438 (m), 1340 (m), 1246 (s), 1213 (m), 1160 (w), 1071 (m), 1036 (m), 1011 (m), 885 (w), 828 (m), 796 (w), 745 (s), 692 (s), 643 (m);

HRMS(ESI) calcd for $C_{11}H_8NO_4^-$ (M-H) 218.0453, found 218.0479.

***tert*-Butyl 2-nitro-2-phenylbut-3-ynoate (13d)**



12d **2** **13d**

The reaction was carried out following general procedure **1** from **12d** (95 mg, 0.40 mmol, 1.0 equiv) and TMS reagent **2** (179 mg, 0.520 mmol, 1.3 equiv). The reaction was quenched after 2.5 h at -78 °C. Purification by flash chromatography (Hexane/EtOAc 20:1) afforded **13d** (89 mg, 0.34 mmol, 85%) as yellow oil.

R*f* 0.66 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 2 H; Ar*H*), 7.47 (m, 3 H; Ar*H*), 3.20 (s, 1 H; C≡C*H*), 1.53 (s, 9 H; OC(CH_3)$_3$);

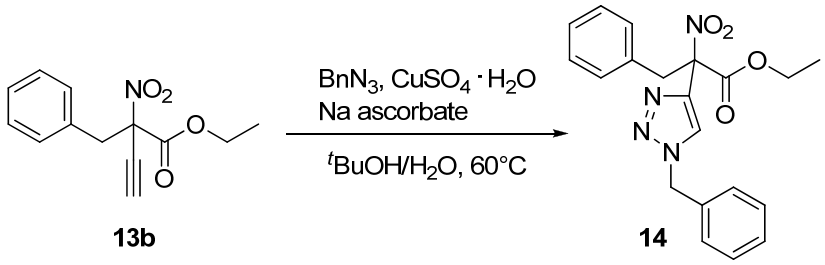
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 131.4, 130.7, 128.8, 128.5, 86.2, 81.9, 77.2, 75.3, 27.5;

IR ν 3288 (w), 2983 (w), 2937 (w), 2362 (w), 2333 (w), 2129 (w), 1754 (s), 1713 (w), 1572 (s), 1494 (w), 1454 (w), 1373 (m), 1343 (w), 1256 (s), 1214 (w), 1152 (s), 1119 (w), 1071 (w), 988 (w), 911 (w), 838 (w), 809 (w), 760 (m), 733 (m), 693 (m);

HRMS(ESI) calcd for $C_{14}H_{14}NO_4^-$ (M-H) 260.0923, found 260.0925.

4. Fonctionalization of New Alkyne Compounds

Ethyl 2-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-nitro-3-phenylpropanoate (14)



13b **14**

Following a slightly modified procedure,[22] Na ascorbate (3.5 mg, 0.017 mmol, 0.10 equiv) and $CuSO_4$ (1 M in water, 1.40 mg, 8.75 μmol, 0.05 equiv) were added sequentially to a stirred solution of **13b** (43 mg, 0.17 mmol, 1 equiv) and benzyl azide (25 μl, 0.17 mmol, 1 equiv) in ^{t}BuOH/H_2O (1:1, 0.60 mL). The reaction mixture was stirred at 60 °C for 18 h. At this time Na ascorbate (10 mg, 0.050 mmol, 0.30 equiv) and $CuSO_4$ (1 M in water, 4.2 mg, 0.026 mmol, 0.15 equiv) were added. The mixture was then additionally stirred 3 h. The mixture was diluted with sat. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residual oil was purified by silica gel flash chromatography (Hexane/EtOAc 10:1) to afford **14** (43 mg, 0.11 mmol, 65%) as yellow solid.

R_f 0.14 (PET/EtOAc 4:1, UV/Anisaldehyde);

Mp 85-89 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1 H; triazole H), 7.36 (m, 3 H; Ar*H*), 7.18 (m, 3 H; Ar*H*), 7.08 (t, *J* = 7.7 Hz, 2 H; Ar*H*), 6.86 (d, *J* = 7.3 Hz, 2 H; Ar*H*), 5.53 (d, *J* = 14.9 Hz, 1 H; NCH_2Ph), 5.48 (d, *J* = 14.9 Hz, 1 H; NCH_2Ph), 4.31 (m, 2 H; OCH_2), 4.27 (d, *J* = 5.1 Hz, 1 H; CH_2Ph), 3.90 (d, *J* = 13.5 Hz, 1 H; CH_2Ph), 1.27 (t, *J* = 7.1 Hz, 3 H; CH_3);

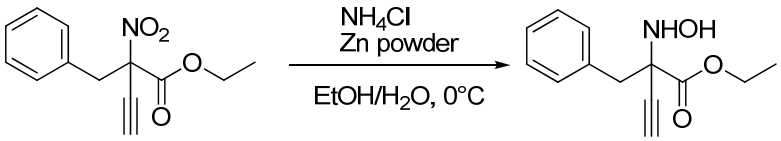
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 141.1, 134.1, 132.6, 130.2, 129.2, 128.9, 128.3, 128.0, 127.8, 126.1, 94.0, 63.4, 54.3, 41.8, 13.8;

IR ν 3164 (w), 3034 (w), 3033 (w), 2985 (w), 2944 (w), 2906 (w), 2361 (w), 2329 (w), 2257 (w), 1952 (w), 1756 (s), 1714 (w), 1668 (w), 1564 (s), 1497 (w), 1456 (w), 1436 (w), 1349 (w), 1240 (m), 1195 (m), 1088 (w), 1049 (m), 1011 (w), 912 (w), 858 (w), 858 (w), 795 (w), 732 (s), 703 (m), 670 (w), 633 (w);

HRMS(ESI) calcd for $C_{20}H_{21}N_4O_4^+$ (M+H) 381.1563, found 381.1556.

[22] W. D. Sharpless, P. Wu, T. V. Hansen, J. G. Lindberg, *J. Chem. Educ.* **2005**, *82*, 1833.

Ethyl 2-benzyl-2-(hydroxyamino)but-3-ynoate (15)



13b **15**

Following a slightly modified procedure,[23] NH_4Cl (1.51 g, 28.3 mmol, 10 equiv) and Zn powder (897 mg, 14.2 mmol, 5 equiv) were sequentially added to a stirred solution of **13b** (700 mg, 2.83 mmol, 1 equiv) in THF (47 mL) and EtOH/H_2O (1:1, 47 mL). The reaction mixture was stirred at 0 °C for 45 min. The mixture was filtered through celite and the filtrate was washed with NaCl. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residual oil was purified by silica gel flash chromatography (Hexane/EtOAc 4:1) to afford **15** (620 mg, 2.65 mmol, 94%) as colorless oil.

R_f 0.2 (PET/EtOAc 4:1, UV/Anisaldehyde);

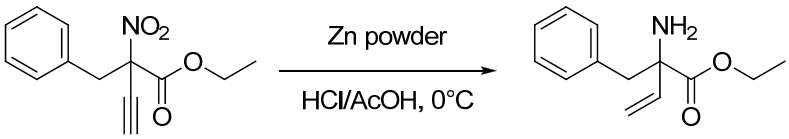
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5 H; Ar*H*), 4.24 (q, *J* = 7.1 Hz, 2 H; OCH_2), 3.21 (d, *J* = 13.4 Hz, 1 H; CH_2Ph), 3.14 (d, *J* = 13.4 Hz, 1 H; CH_2Ph), 2.52 (s, 1 H; C≡C*H*), 1.26 (t, *J* = 7.1 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 133.9, 130.4, 128.3, 127.5, 80.2, 75.0, 66.7, 62.5, 41.3, 14.0;

IR ν 3283 (w), 3039 (w), 3031 (w), 2983 (w), 2940 (w), 2864 (w), 2361 (m), 2343 (w), 2140 (w), 1737 (s), 1605 (w), 1498 (w), 1457 (w), 1376 (w), 1369 (w), 1268 (m), 1235 (m), 1087 (w), 1034 (m), 920 (w), 857 (w), 741 (s), 702 (s), 680 (m), 671 (m), 653 (m), 626 (s), 611 (m);

HRMS(ESI) calcd for $C_{13}H_{16}NO_3^+$ (M+H) 234.1130, found 234.1140.

E**thyl 2-amino-2-benzylbut-3-enoate (16)**



13b **16**

Following a slightly modified procedure,[24] Zn powder (0.23 g, 3.5 mmol, 38 equiv) was added to a stirred solution of **12b** (20 mg, 0.081 mmol, 1 equiv) in 1 N HCl/AcOH (2:1, 0.75 mL) at 0 °C. The reaction mixture was stirred for 2 days and monitored by TLC analysis (PET/EtOAc 4:1, UV and *p*-anisaldehyde). The mixture was then filtered through cotton and washed with CH_2Cl_2 (3x10 mL). 1 M NaOH solution was added until PH≈11-12. The two layers were separated and the aqueous layer was washed with CH_2Cl_2 (3x10 mL).. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residual yellow oil was purified by silica gel flash chromatography (Hexane/EtOAc 4:1) to afford **16** (10 mg, 0.046 mmol, 57%) as colorless oil.

R_f 0.2 (PET/EtOAc 4:1, UV/Anisaldehyde);

[23] C. Y. Jin, J. P. Burgess, J. A. Kepler, C. E. Cook, *Org. Lett.* **2007**, *9*, 1887.
[24] W. Oppolzer,O. Tamura, J. Deerberg, *Helv. Chim. Acta* **1992**, *75*, 1965.

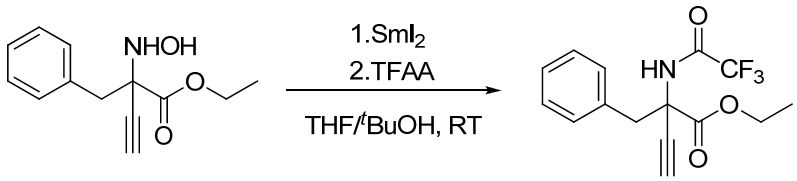
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3 H; Ar*H*), 7.20 (m, 2 H; Ar*H*), 6.21 (dd, *J* = 17.3, 10.6 Hz, 1 H; CH_2=C*H*), 5.37 (d, *J* = 17.3 Hz, 1 H; CH_2=CH), 5.22 (d, *J* = 10.6 Hz, 1 H; CH_2=CH), 4.20 (q, *J* = 7.1 Hz, 2 H; OCH_2), 3.30 (d, *J* = 13.2 Hz, 1 H; CH_2Ph), 2.87 (d, *J* = 13.2 Hz, 1 H; CH_2Ph), 1.74 (br s, 2 H; NH_2), 1.30 (t, *J* = 7.1 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, CD_2Cl_2) δ 174.5, 140.6, 135.9, 130.0, 128.0, 126.7, 113.8, 61.2, 45.6, 29.5, 13.8;

IR ν 2957 (m), 2937 (m), 2926 (s), 2855 (m), 2361 (w), 2338 (w), 1734 (s), 1638 (w), 1601 (w), 1461 (w), 1376 (w), 1375 (w), 1374 (w), 1277 (w), 1189 (w), 1082 (w), 1031 (w), 998 (w), 927 (w), 866 (w), 865 (w), 847 (w), 846 (w), 781 (w), 743 (w), 742 (w), 705 (m), 673 (w), 665 (m), 649 (w), 638 (s), 617 (w);

HRMS (ESI) calcd for $C_{13}H_{18}NO_2^+$ (M+H) 220.1338, found 220.1346.

Ethyl 2-benzyl-2-(2,2,2-trifluoroacetamido)but-3-ynoate (17)



15 **17**

To a stirred solution of ^{t}BuOH (1 mL) and THF (2 mL) was added **15** (50 mg, 0.21 mmol, 1 equiv) under N_2 at RT. The mixture was stirred for 5 min and then SmI_2 (0.1 M in THF, 12.8 mL, 1.28 mmol, 6 equiv) was slowly added at RT. The blue mixture was stirred 20 min and then TFAA (90 μL, 0.64 mmol, 3 equiv) was added. The resulting yellow mixture was stirred 30 min at RT. After this time, the mixture was diluted with Et_2O and washed with brine. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residual oil was purified by deactivated silica gel flash chromatography (Hexane/EtOAc 10:1) to afford **17** (44 mg, 0.14 mmol, 67%) as yellow liquid.

R_f 0.4 (PET/EtOAc 4:1, UV/Anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3 H; Ar*H*), 7.08 (m, 2 H; Ar*H*), 4.35 (m, 2 H; OCH_2), 3.80 (d, *J* = 13.9 Hz, 1 H; CH_2Ph), 3.50 (d, *J* = 13.9 Hz, 1 H; CH_2Ph), 2.62 (s, 1 H; C≡C*H*), 1.38 (t, *J* = 7.2 Hz, 3 H; CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 155.7 (q, $J_{1,3}$(C,F) = 38 Hz; *C*OCF_3), 133.3, 129.8, 128.6, 128.0, 115.2 (q, $J_{1,2}$ (C,F) = 288 Hz; CF_3), 78.3, 74.5, 63.8, 57.9, 41.3, 13.9;

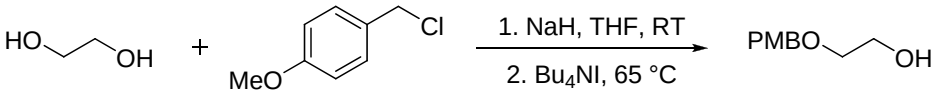
IR ν 3380 (w), 3304 (w), 3067 (w), 3035 (w), 2987 (w), 2967 (w), 2904 (w), 2360 (m), 2343 (m), 2126 (w), 1731 (s), 1523 (m), 1498 (w), 1457 (w), 1445 (w), 1396 (w), 1373 (w), 1266 (m), 1212 (s), 1168 (s), 1086 (w), 1040 (w), 1008 (w), 912 (w), 894 (w), 861 (w), 771 (w), 740 (m), 703 (m), 687 (w), 668 (w), 658 (m), 646 (w), 628 (w), 620 (w);

HRMS(ESI) calcd for $C_{15}H_{15}NO_3F_3^+$ (M+H) 314.1004, found 314.1014.

5. Mechanistic Investigations

5.1 Preparation of ^{13}C-labeled reagent 18.

2-(4-Methoxybenzyloxy)ethanol (50)



48 **49** **50**

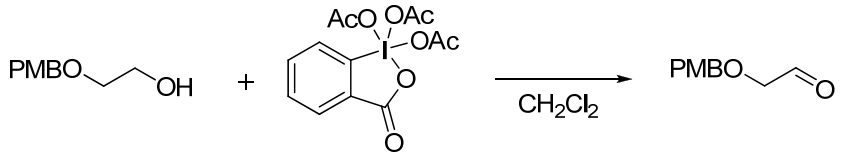
Following a reported procedure,[25] sodium hydride (60% in mineral oil, 0.70 g, 17 mmol, 1.0 equiv) was added to a solution of ethylene glycol (**48**) (freshly distilled from drierite (p = 0.3 mbar, T = 46 °C), 2.8 mL, 50 mmol, 3.0 equiv) in THF (30 mL). After stirring 30 min at RT, 4-methoxybenzyl chloride (**49**) (2.60 g, 16.6 mmol, 1.00 equiv) and Bu_4NI (0.61 g, 1.7 mmol, 0.10 equiv) were added, and the reaction mixture was heated to reflux. After 4.5 h, the reaction mixture was cooled to RT, the reaction was quenched with sat. NH_4Cl (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt, 5/1, 1/1) to yield protected alcohol **50** (2.54 g, 13.9 mmol, 84%) as a yellow oil.

R_f 0.25 (PET/AcOEt, 1:1, UV/$KMnO_4$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (dm, *J*= 8.2 Hz, 2 H; Ar*H*), 6.89 (dm, *J*= 8.6 Hz, 2 H; Ar*H*), 4.49 (s, 2 H; benzyl CH_2), 3.81 (s, 3 H; OCH_3), 3.74 (t, *J*= 4.3 Hz, 2 H; CH_2OPMB), 3.57 (m, 2 H; CH_2OH), 2.08 (br s, 1 H; O*H*).

^{1}H NMR corresponded to the literature values.[16]

2-(4-Methoxybenzyloxy)acetaldehyde (52)



50 **51** **52**

Following a reported procedure,[26] Dess-Martin Periodinane (**51**) (0.53 g, 1.3 mmol, 1.1 equiv) was added to a solution of alcohol **50** (0.21 g, 1.2 mmol, 1.0 equiv) in wet CH_2Cl_2 (9 mL). After stirring 2.5 h at RT, the reaction was quenched with sat. $NaHCO_3$ (10 mL) and sat. sodium thiosulfate solution (10 mL) and the mixture was stirred vigorously for 10 min until two clear layers were obtained. The layers were separated and the water layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give aldehyde **52** (0.21 g, 1.2 mmol, quant.) as a yellow oil, which was used immediately in the next step without further purification.

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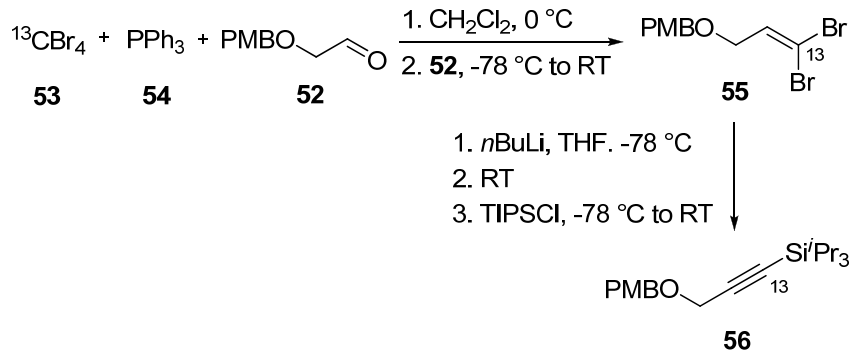
[25] K. Masutani, T. Minowa, Y. Hagiwara, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106.
[26] I. Collins, J. Caldwell, T. Fonseca, A. Donald, V. Bavetsias, L. J. K. Hunter, M. D. Garrett, M. G. Rowlands, G. W. Aherne, T. G. Davies, V. Berdini, S. J. Woodhead, D. Davis, L. C. A. Seavers, P. G. Wyatt, P. Workman, E. McDonald, *Bioorg. Med. Chem.* **2006**, *14*, 1255.

R_f 0.35 (PET/AcOEt 1:1, UV/$KMnO_4$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.71 (t, *J*= 0.9 Hz, CHO), 7.29 (dm, *J*= 8.8 Hz, 2 H; ArH), 6.90 (dm, *J*= 8.8 Hz, 2 H; ArH), 4.57 (s, 2 H; benzyl CH_2), 4.07 (d, *J*= 0.9 Hz, 2 H; CH_2CHO), 3.81 (s, 3 H; OCH_3).

^{1}H NMR corresponded to the literature values.[17]

Labeled 1-((3,3-dibromoallyloxy)methyl)-4-methoxybenzene (55) and tri*iso*-propyl(3-(4-methoxybenzyloxy)prop-1-ynyl)silane (56)



Following a slightly modified literature procedure,[27] a solution of PPh_3 (**54**) (1.6 g, 6.0 mmol, 2.0 equiv) in CH_2Cl_2 (9 mL) was added to a solution of CBr_4 (**53**) (1.0 g, 3.0 mmol, 1.0 equiv, 20% ^{13}C, prepared from 0.80 g natural CBr_4 and 0.20 g 99% ^{13}C-enriched CBr_4) in CH_2Cl_2 (12 mL) at 0 °C over 15 min. After stirring for 15 min at 0 °C, the yellow-orange solution was cooled to –78 °C and a solution of aldehyde **52** (freshly synthesized, 0.66 g, 3.6 mmol, 1.2 equiv) in CH_2Cl_2 (9 mL) was added over 10 min, whereas the reaction mixture turned dark red-brown. The reaction mixture was left to warm to RT over 17 h, quenched with sat. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/CH_2Cl_2, 3:1, 1.5:1) to yield dibromide **55** (501 g, 1.55 mmol, 52%) as a slightly yellow oil, which was used directly in the next step.

R_f 0.30 (PET/ CH_2Cl_2 2:1, UV/$KMnO_4$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (dm, *J*=8.6 Hz, 2 H; Ar*H*), 6.90 (dm, *J*= 8.6 Hz, 2 H; Ar*H*), 6.64 (tm, *J*= 6.1 Hz, 1 H; alkene *H*), 4.46 (s, 2 H; benzyl CH_2), 4.04 (m, 2 H; alkene CH_2), 3.81 (s, 3 H; OCH_3);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 135.6, 129.5, 129.4, 113.8, 91.3 (labeled 20x more intensive), 72.2, 69.4, 55.2;

Following a literature procedure,[28] *n*BuLi (2.5 M in hexane, 1.4 mL, 3.4 mmol, 2.2 equiv) was added dropwise to a solution of dibromide **55** (0.50 g, 1.5 mmol, 1.0 equiv) in THF (9 mL) at –78 °C. The yellow solution was stirred 1 h at –78 °C and 1 h at RT. After cooling to –78 °C, TIPSCl (0.43 mL, 2.0 mmol, 1.3 equiv) was added and the reaction was left to warm to RT over 12 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/CH_2Cl_2, 4:1, 2:1) to yield alkyne **56** (372 g, 1.12 mmol,

[27] L. A. Paquette, J. Y. Chang, Z. S. Liu, *J. Org. Chem.* **2004**, *69*, 6441.
[28] E. J. Corey, P. L Fuchs,. *Tetrahedron Lett.* **1972**, 3769.

72%) as a colorless oil. Comparison of the ^{13}C NMR with an unlabeled sample (synthesized following the same procedure) showed 20% ^{13}C incorporation at the indicated position only.

R_f 0.35 (PET/CH_2Cl_2 2:1, UV/$KMnO_4$);

^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (dm, *J*= 8.4 Hz, 2 H; Ar*H*), 6.89 (dm, *J*= 8.6 Hz, 2 H; Ar*H*), 4.59 (s, 2 H; benzyl CH_2), 4.19 (s, 2 H; alkyne CH_2), 3.81 (s, 3 H; OCH_3), 1.12 (m, 21 H; TIPS);

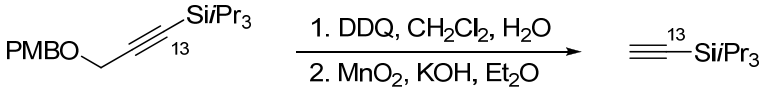
^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 129.8, 129.5, 113.8, 103.4, 87.7 (labeled 20x more intensive), 70.6, 57.4, 55.2, 18.6, 11.1;

IR ν 2961 (w), 2944 (w), 2931 (w), 2866 (w), 2171 (w), 1663 (w), 1614 (w), 1515 (w), 1463 (w), 1444 (w), 1378 (w), 1250 (w), 1078 (m), 1036 (w), 907 (s), 730 (s), 651 (m);

HRMS(ESI) calcd for $C_{15}H_{16}O_3^+$ (M+H) 333.2250, found 333.2254.

Isotope repartition: expected for about 20% incorporation was obtained.

Labeled tri*iso*-propyl acetylene (57)



56 **57**

Following a literature procedure,[29] DDQ (0.38 g, 1.7 mmol, 1.5 equiv) was added to a solution of protected alcohol **56** (372 mg, 1.12 mmol, 1.00 equiv) in CH_2Cl_2 (11 mL) and water (1.1 mL) at 0 °C. The reaction mixture was stirred 15 min at 0 °C and 3 h at RT. The resulting dark red thick suspension was quenched with sat. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. TLC (PET/AcOEt 6:1, $KMnO_4$) showed a mixture of two products, which were shown to be the corresponding propargylic alcohol (R_f = 0.50) and anisaldehyde (R_f = 0.45) by ^1H NMR. This mixture was directly used as such in the next step.

Following a literature procedure,[30] the obtained mixture was diluted in Et_2O (14 mL) and MnO_2 (Aldrich activated, 1.2 g, 13 mmol, 12 equiv) and KOH (freshly grounded, 0.38 g, 6.8 mmol, 6.0 equiv) were added in 4 portions every hour. After stirring for further 3 h, TLC (PET/AcOEt 6:1, $KMnO_4$) showed complete conversion and the reaction mixture was filtered over SiO_2 and the filter cake was washed with Et_2O (50 mL). The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (PET) to yield alkyne **57** (167 mg, 0.915 mmol, 82%) as a colorless oil. Comparison of the ^{13}C NMR with an unlabeled sample (synthesized following the same procedure) showed 20% ^{13}C incorporation at the indicated position only.

R_f 0.80 (PET, UV/$KMnO_4$);

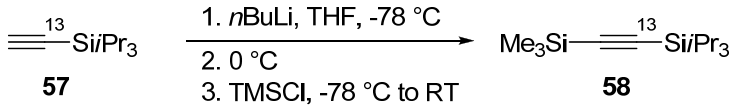
^1H NMR (CD_2Cl_2, 400 MHz) δ 2.38 (s, 1 H; alkyne *H*), 1.07 (m, 21 H; TIPS);

[29] P. Dimopoulos, A. Athlan, S. Manaviazar, J. George, M. Walters, L. Lazarides, A. E. Aliev, K. J. Hale, *Org. Lett.* **2005**, *7*, 5369.

[30] H. Kukula, S. Veit, A. Godt, *Eur. J. Org. Chem.* **1999**, 277.

^{13}C NMR (CD_2Cl_2, 100 MHz) δ 94.9, 86.2 (labeled 20x more intensive), 18.3, 11.1.

Labeled tri*iso*-propyl((trimethylsilyl)ethynyl)silane (58)



*n*BuLi (2.5 M in hexane, 0.44 mL, 1.1 mmol, 1.2 equiv) was added to a solution of acetylene **57** (167 mg, 0.915 mmol, 1.00 equiv) in THF (2 mL) at –78 °C. The reaction mixture was stirred 15 min at 0 °C and the yellow solution was cooled back to –78 °C. TMSCl (freshly distilled, 0.15 mL, 1.2 mmol, 1.3 equiv) was added and the colorless solution was left to warm to RT over 6 h. The reaction was quenched with sat. NH_4Cl (3 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (PET) to yield protected alkyne **58** (184 g, 0.722 mmol, 79%) as a colorless oil. Comparison of the ^{13}C NMR with an unlabeled sample showed 20% ^{13}C incorporation at the indicated position only.

R_f 0.80 (PET, UV/$KMnO_4$);

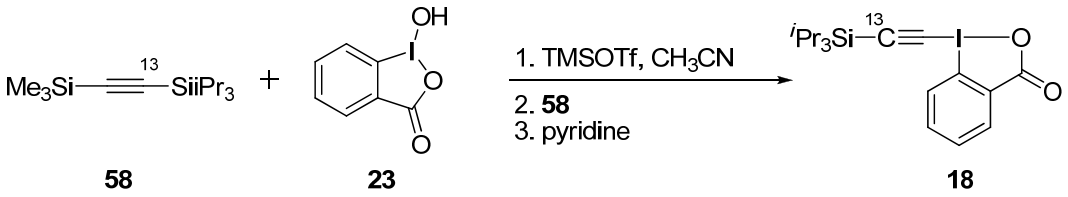
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (m, 21 H; TIPS), 0.17 (s, 9 H; TMS);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 116.2, 110.1 (labeled 20x more intensive), 18.6, 11.1, 0.0;

IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m).

^{1}H NMR corresponded to the literature values.[31]

Labeled 1-[(tri*iso*--propyllsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (18)



Following a slightly modified literature procedure,[3] TMSOTf (freshly distilled, 0.15 mL, 0.82 mmol, 1.1 equiv) was added to a suspension of iodinane **23** (freshly synthesized, 0.19 g, 0.72 mmol, 1.0 equiv) in CH_3CN (6.5 mL). After 10 min, a solution of acetylene **58** (0.18 g, 0.72 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added to the slightly yellow solution. After stirring 15 min at RT, pyridine (70 µL, 0.87 mmol, 1.2 equiv) was added and the solvent was removed under reduced pressure below 30 °C. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with 1 M HCl (5 mL). The water layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were washed with sat. Na_2CO_3 (2 x 10 mL). The combined basic aqueous layers were extracted with CH_2Cl_2 (10 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give iodinane **18** (>95% pure by ^{1}HNMR, containing traces of acetylene **57**, 259 mg, 0.604 mmol, 84%) as a slightly yellow solid.

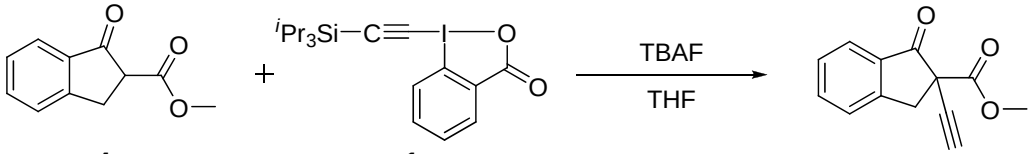
[31] C J. Helal, P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 10938.

Comparison of the ^{13}C NMR with an unlabeled sample showed 20% ^{13}C incorporation at the indicated position only.

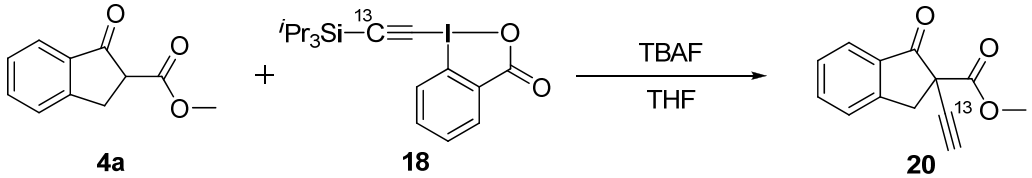
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (m, 1 H; Ar*H*), 8.28 (m, 1 H; Ar*H*), 7.74 (m, 2 H; Ar*H*), 1.13 (m, 21 H; TIPS);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 134.6, 132.4, 131.5, 131.4, 126.0, 115.6, 114.1 (labeled 20x more intensive), 64.7, 18.4, 11.1.

5.2 Reaction of ^{13}C-labeled reagent 18

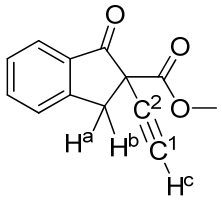


The reaction was carried out following general procedure **1** using **4a** (76 mg, 0.40 mmol, 1.00 equiv), TIPS reagent **1** (220 mg, 0.520 mmol, 1.3 equiv) and TBAF (520 µL, 0.520 mmol, 1.3 equiv). The reaction was stirred at -78 °C during 5 h and warm up to 10 °C over 9.5 h before quenching. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 20:1) afforded **5a** (69 mg, 0.32 mmol, 80%) as a yellow solid.



The reaction was carried out following general procedure **1** from **4a** (76 mg, 0.40 mmol, 1.00 equiv), TIPS reagent **1** (0.11 g, 0.26 mmol, 0.65 equiv) and labeled reagent **18** (0.11 g, 0.26 mmol, 0.65 equiv). The reaction was stirred at -78 °C during 5 h and warm up to 10 °C over 13 h before quenching. Purification by flash chromatography using deactivated silicagel (Hexane/EtOAc 20:1) afforded **20** (67 mg, 0.31 mmol, 78%) as a yellow solid.

R_f 0.33 (PET/Et_2O 4:1, UV/Anisaldehyde);



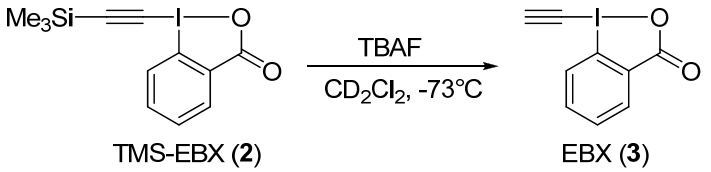
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.7, 0.3 Hz, 1 H; Ar*H*), 7.65 (td, *J* = 7.6, 1.2 Hz, 1 H; Ar*H*), 7.49 (d, *J* = 7.7 Hz, 1H; Ar*H*), 7.42 (m, 1 H; Ar*H*), 3.92 (d, *J* = 17.1 Hz, 1 H; CH_2, **H^a** or **H^b**), 3.78 (s, 3H; CH_3), 3.51 (d, *J* = 17.1 Hz, 1 H; CH_2, **H^a** or **H^b**), 2.42 (s, 1 H; C≡C*H,* **H^c**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 168.1, 152.1, 136.0, 133.0, 128.2, 126.3, 125.7, 79.8 (**C^2**, labeled 10x more intensive), 72.3 (**C^1**), 55.2, 53.8, 40.4;

Comparison of the ^{13}C NMR with an unlabeled sample showed 10% ^{13}C incorporation at the $\mathbf{C^2}$ position only. Assignment of $\mathbf{C^1}$ and $\mathbf{C^2}$ was confirmed with 2D NMR experiments. In particular, the coupling between $\mathbf{C^1}$ and $\mathbf{H^c}$ was stronger than between $\mathbf{C^2}$ and $\mathbf{H^c}$ in the HSQC experiment and only $\mathbf{C^2}$ show a coupling with $\mathbf{H^a}$ or $\mathbf{H^b}$ in HMBC experiment.

5.3 Low temperature NMR experiments: Detection of EBX (3)

1-Ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX, 3)



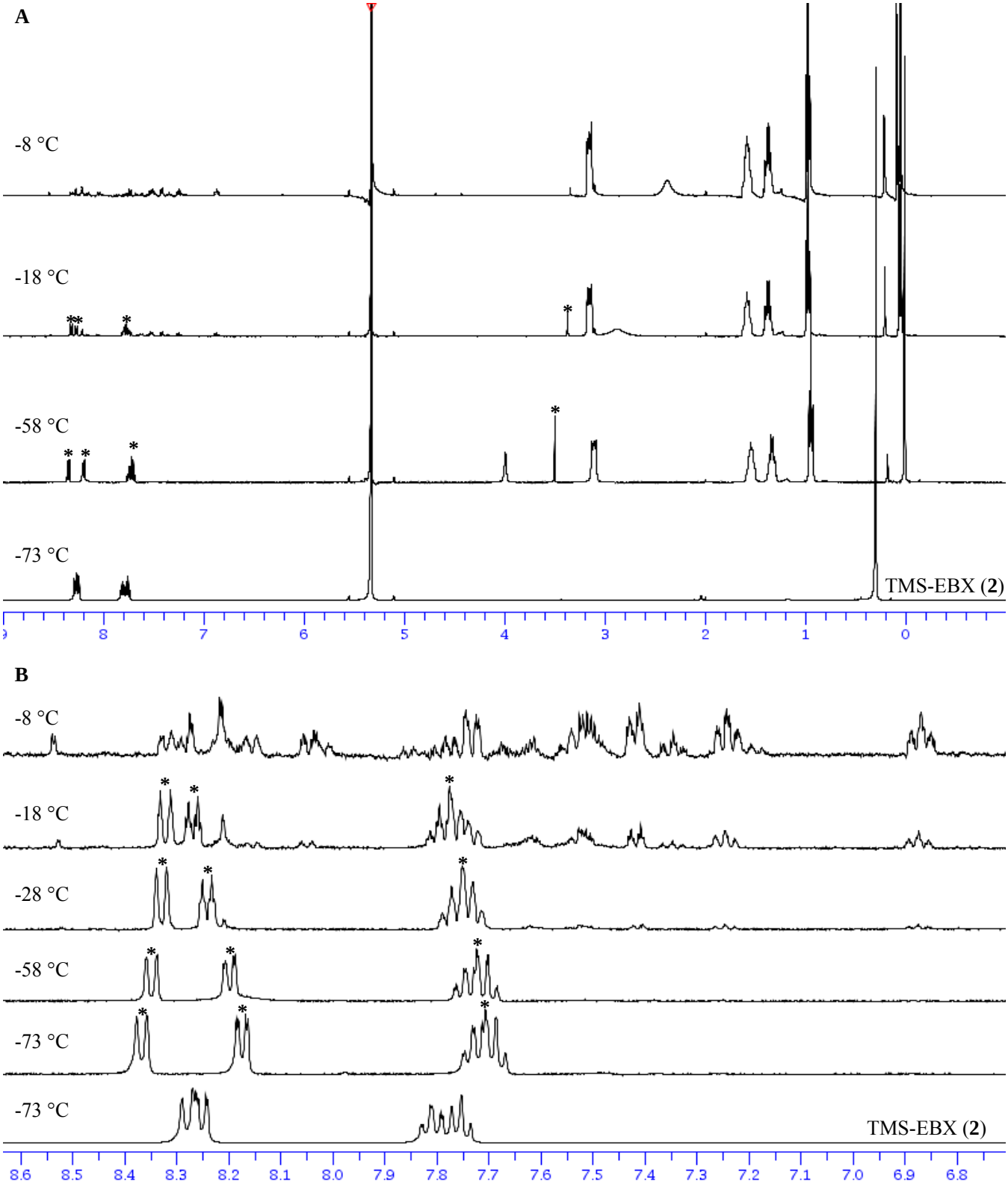
TMS-EBX (**2**) EBX (**3**)

A solution of TMS-EBX (**2**) (13 mg, 0.038 mmol, 1.0 equiv) in CD_2Cl_2 (0.80 mL) was cooled to -78 °C. A cooled (-78 °C) solution of TBAF•$3H_2O$ (11.9 mg, 0.0380 mmol, 1.0 equiv) in CD_2Cl_2 (0.15 mL) was added and the reaction was monitored by ^1H NMR from -73 °C to -8 °C (Figure S1). Decomposition of the reagent started around -20 °C and was completed at -8 °C. A ^{13}C NMR spectra could be obtained at -78 °C over night. Furthermore, a temperature-dependent shift of the signals was observed in ^1H NMR, as well as signal broadening in ^{13}C NMR, indicating some dynamic phenomena.

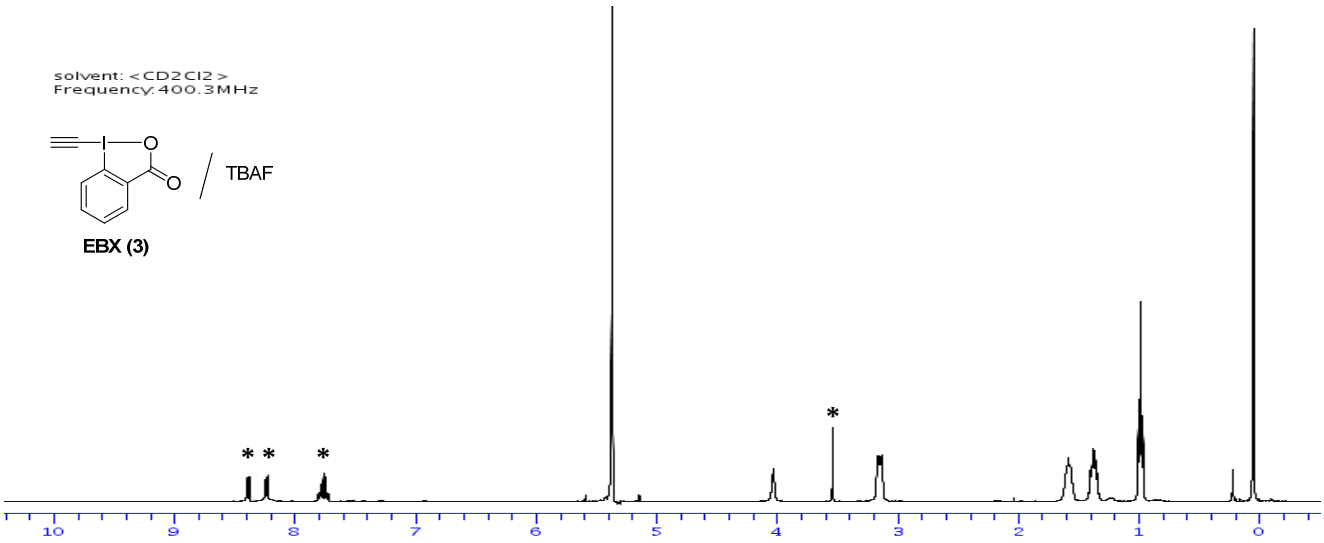
^1H NMR (CD_2Cl_2, 400 MHz, -58 °C) δ 8.35 (d, 1 H, J = 8.1 Hz, Ar H), 8.20 (dd, 1 H, J = 7.1, 1.6 Hz, Ar H), 7.74 (m, 2 H, Ar H), 3.50 (s, 1 H).

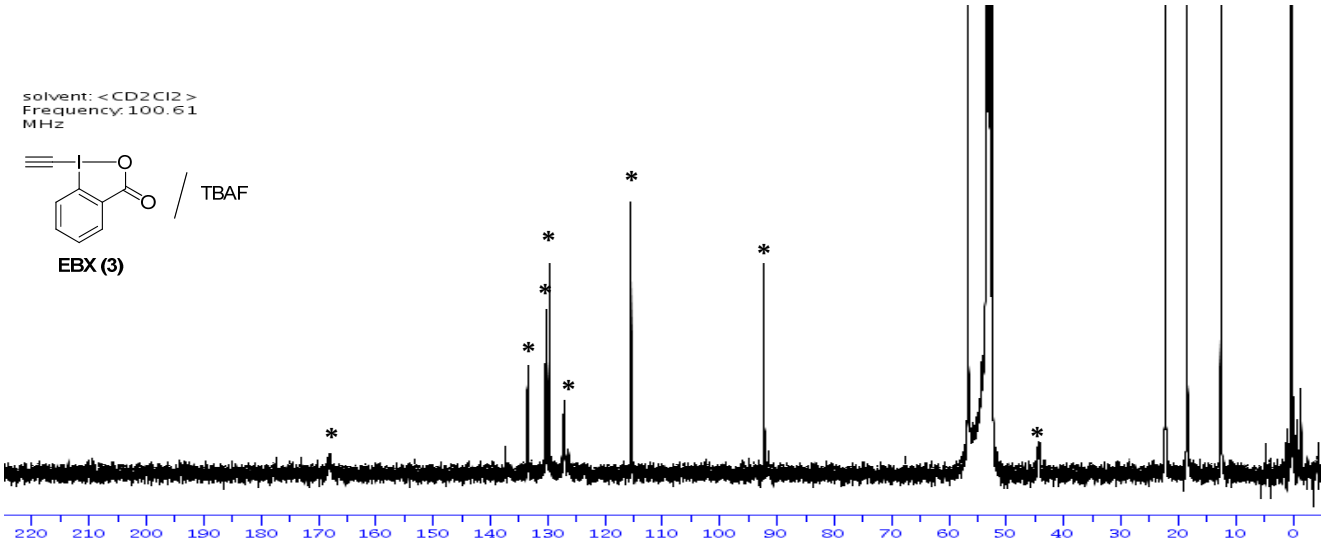
^{13}C NMR (CD_2Cl_2, 100 MHz, -78 °C) δ 168.2 (br m), 133.4 (br m), 130.4 (br m), 130.3 (br m), 129.8 (br m), 127.2 (br m), 115.5, 92.3, 44.3 (br m).

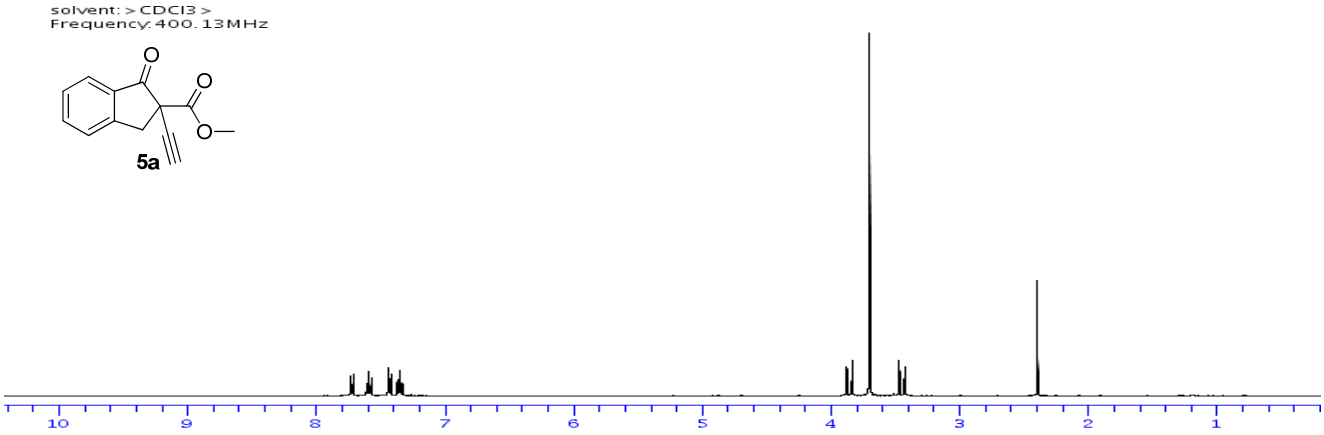
Figure S1. Generation and decomposition of EBX (**3**): **A** full spectra (400 MHz, CD_2Cl_2), **B** aromatic region. EBX (3) signals are indicated by a *. Other signals comes from TBAF and Me_3SiX.



6. Spectra of New Compounds



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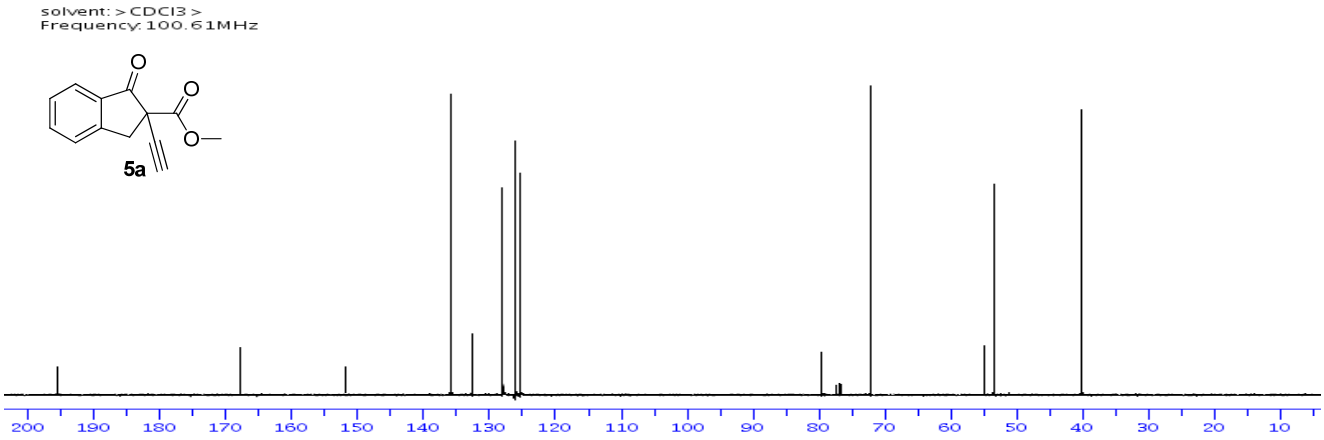
1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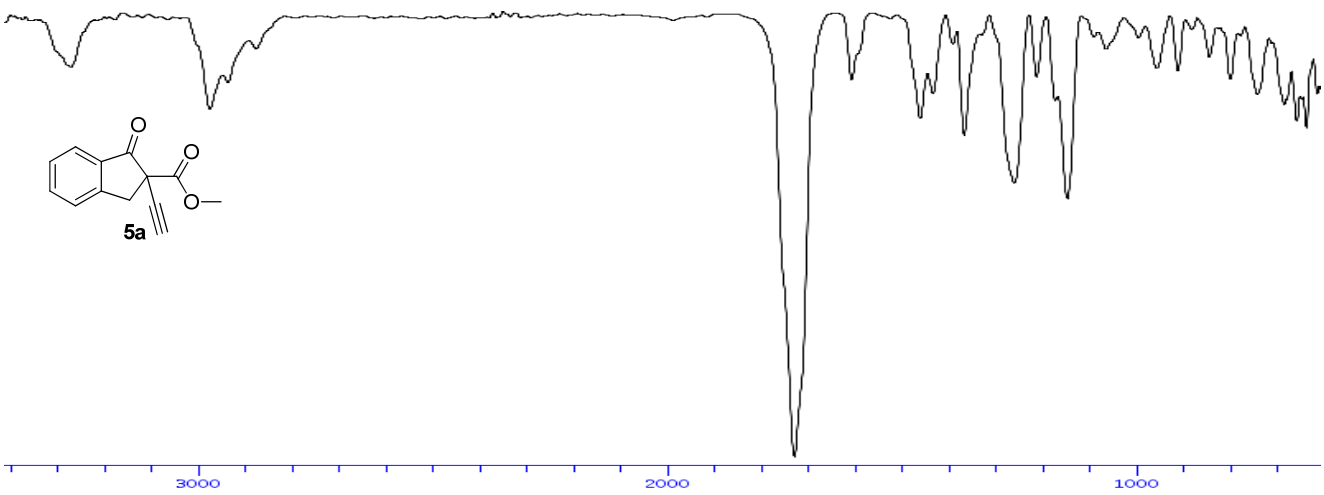
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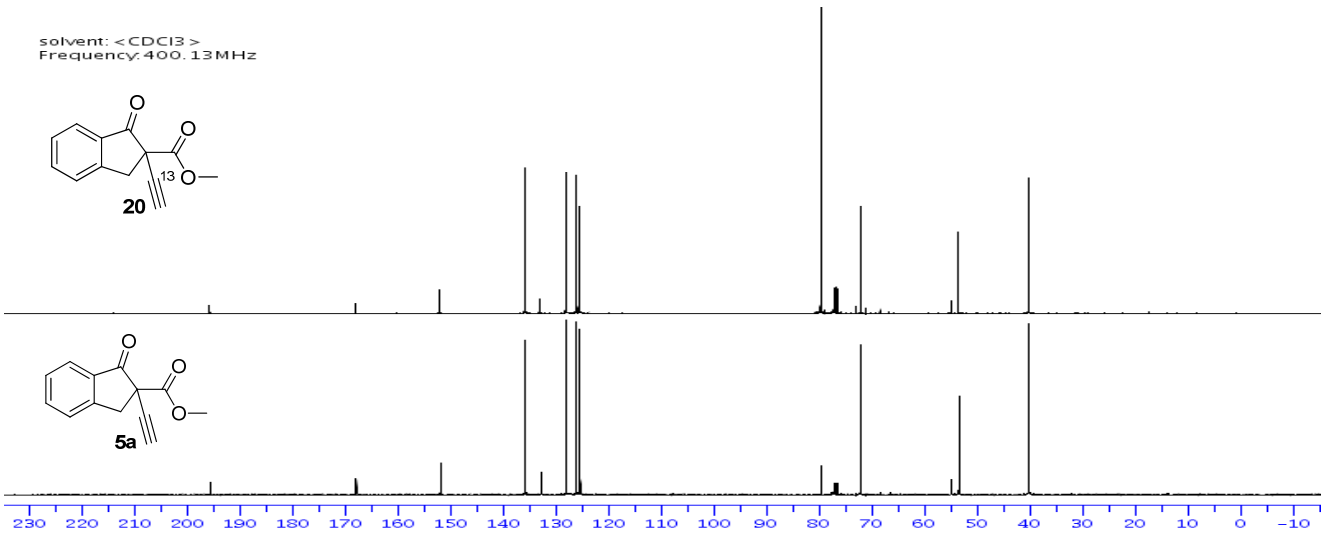
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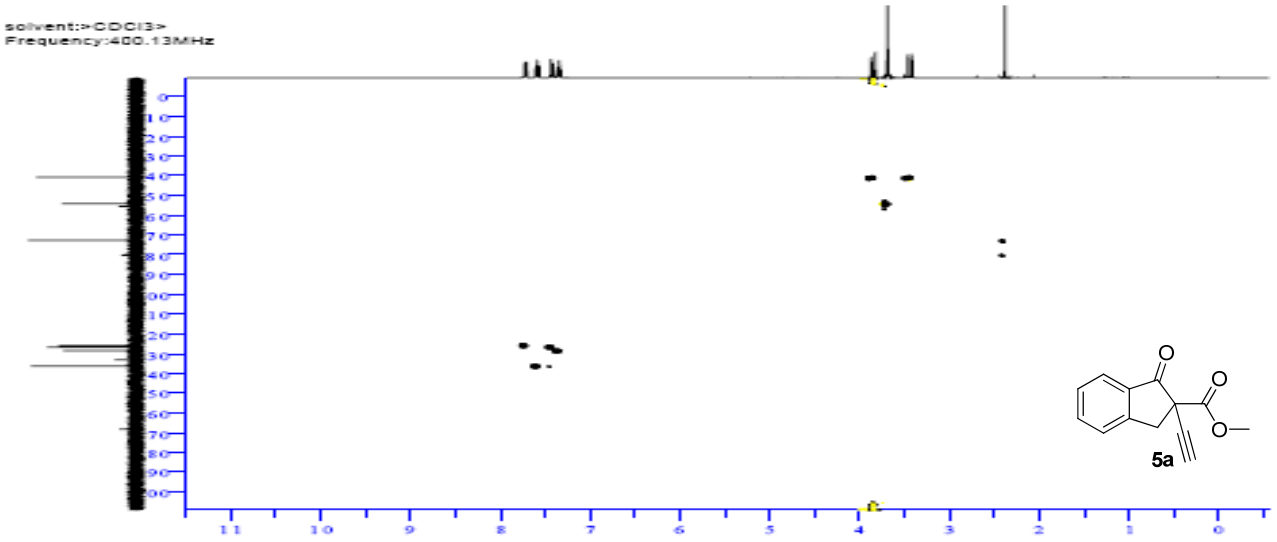
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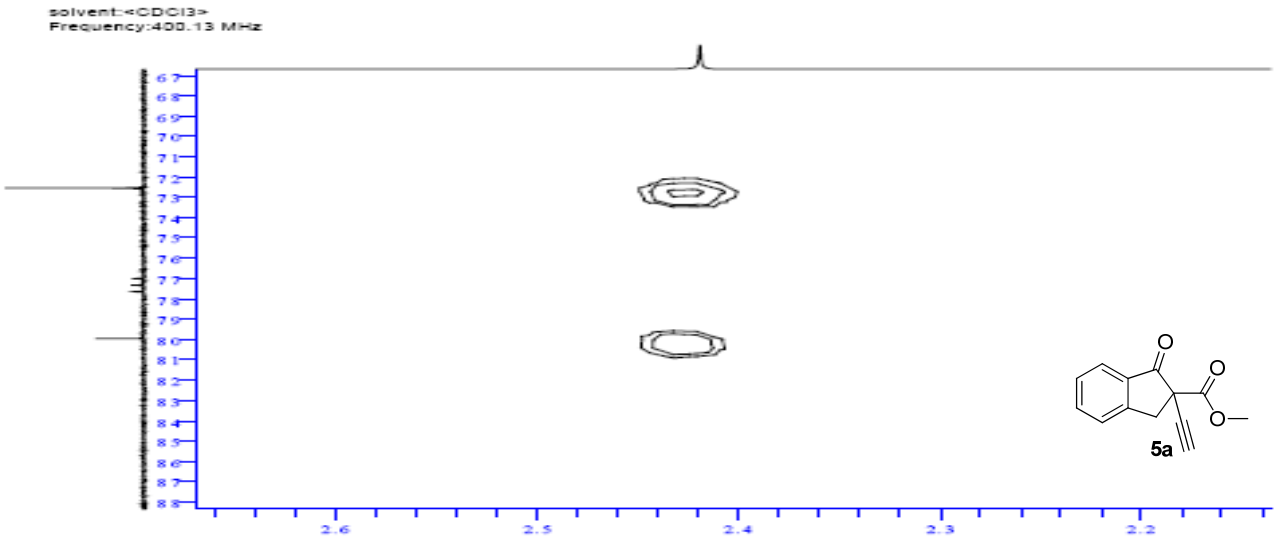
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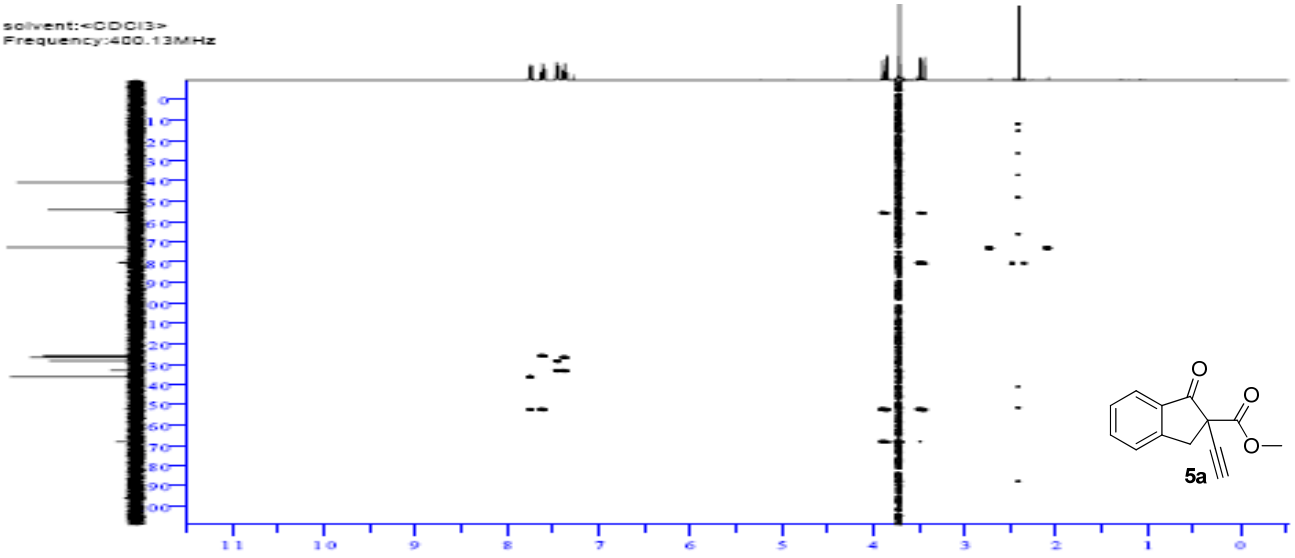
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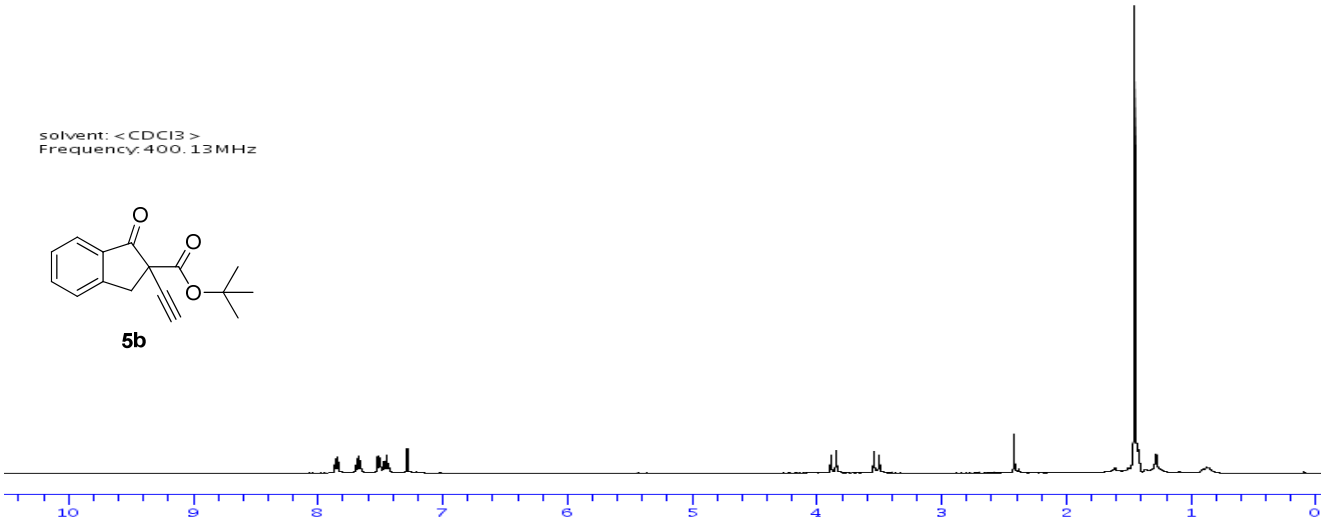
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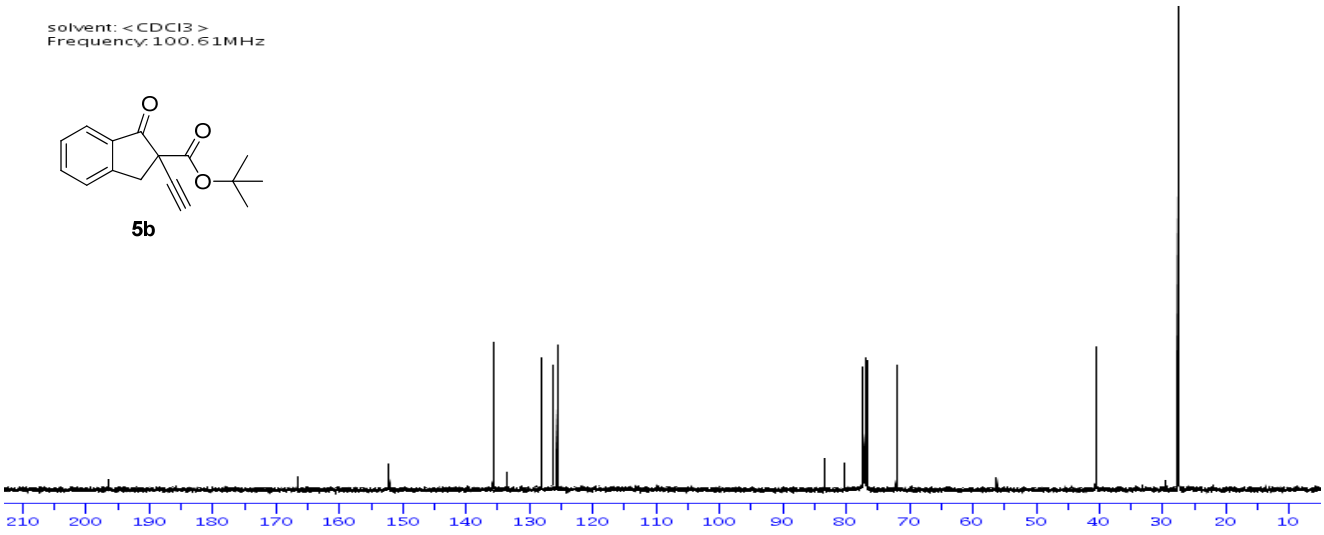
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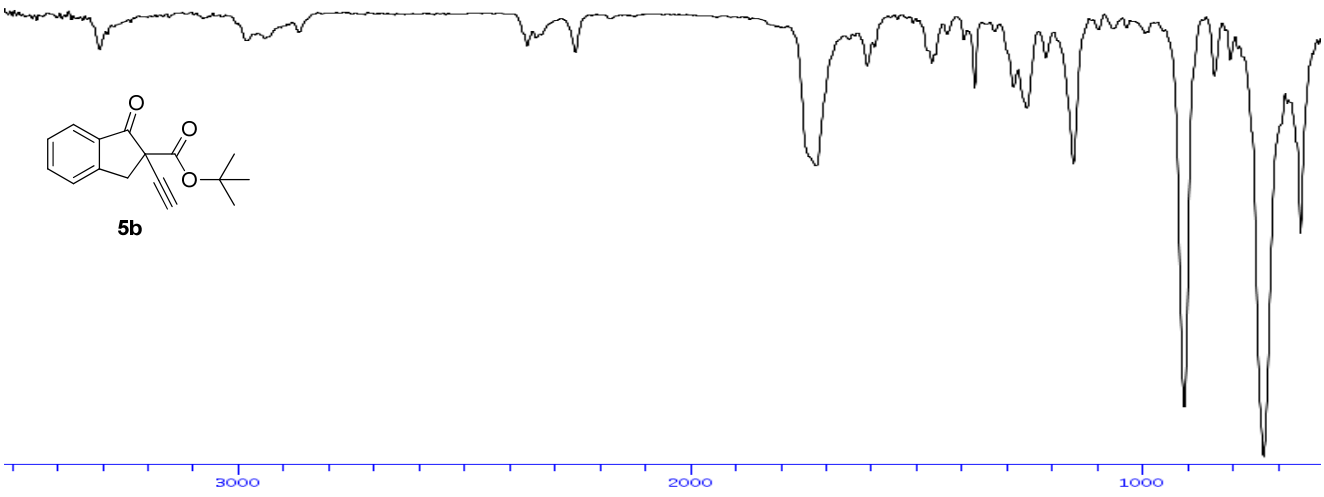
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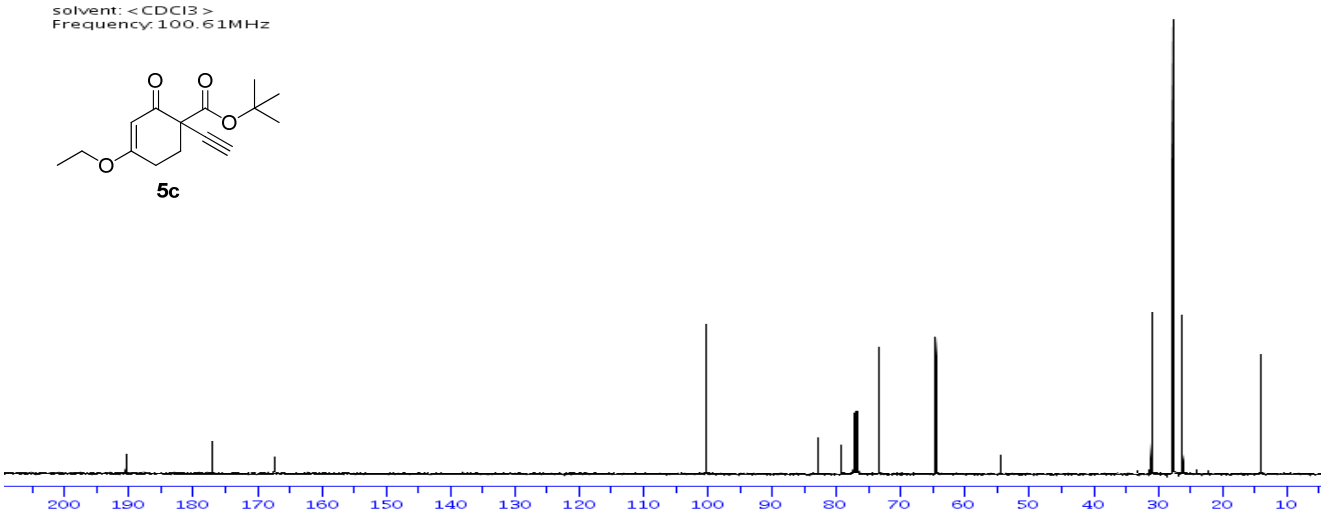
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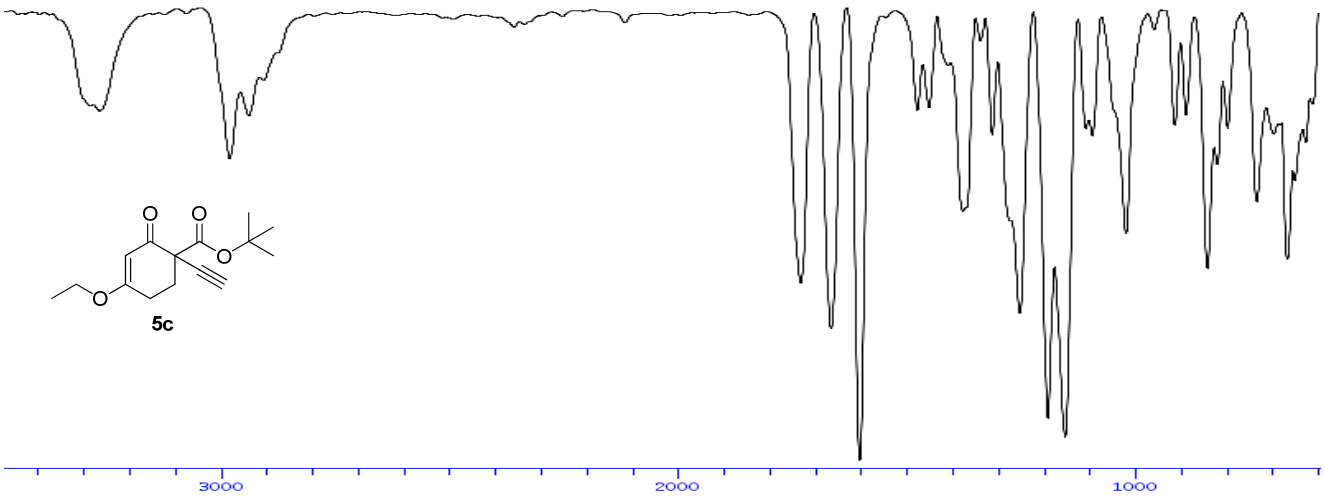
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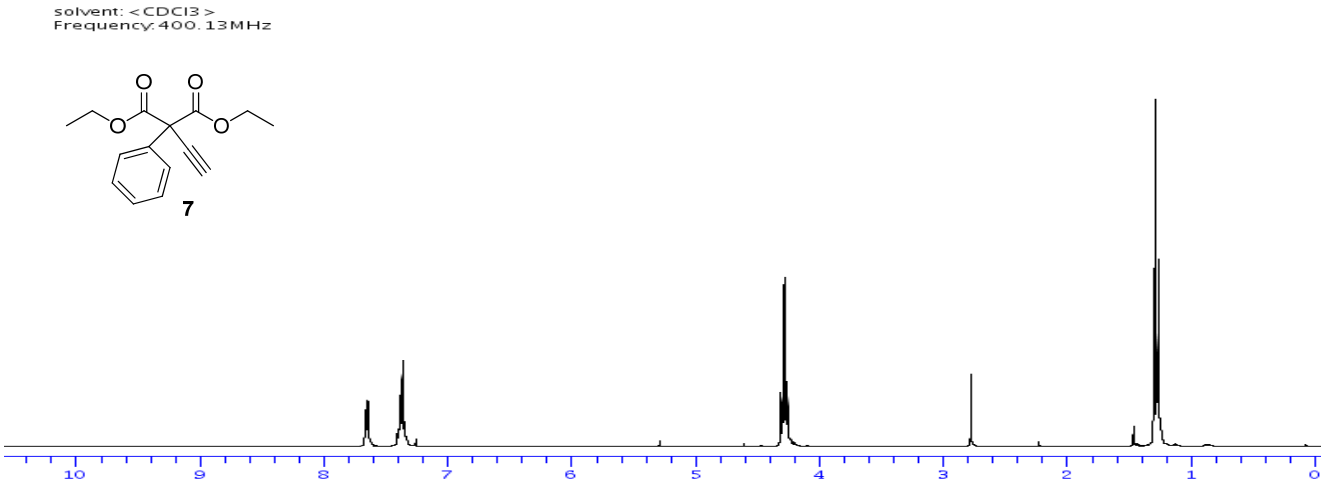
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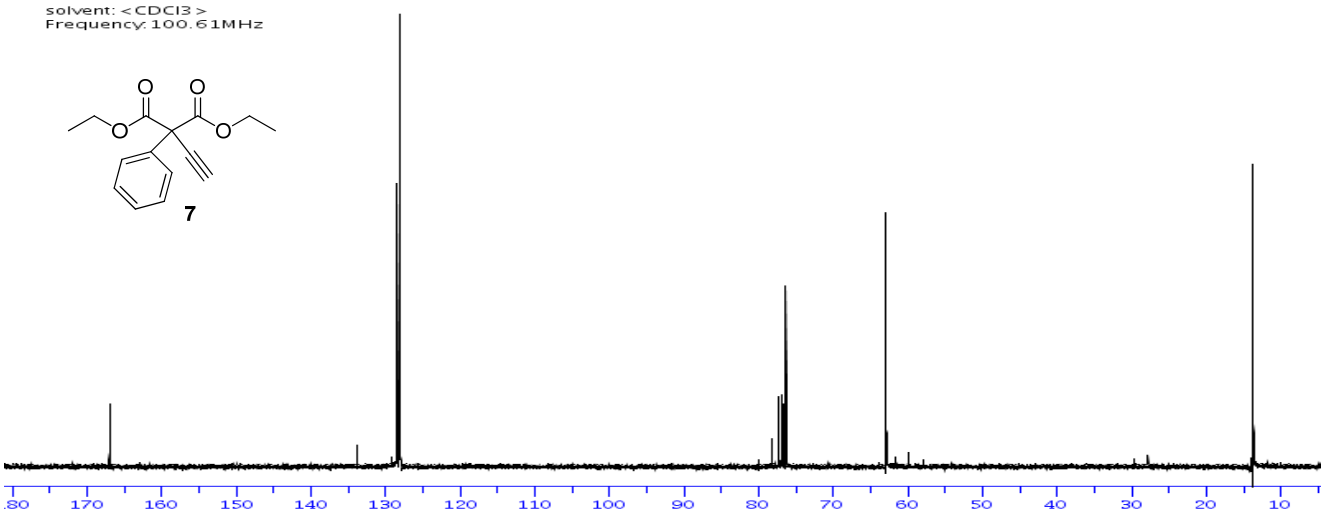
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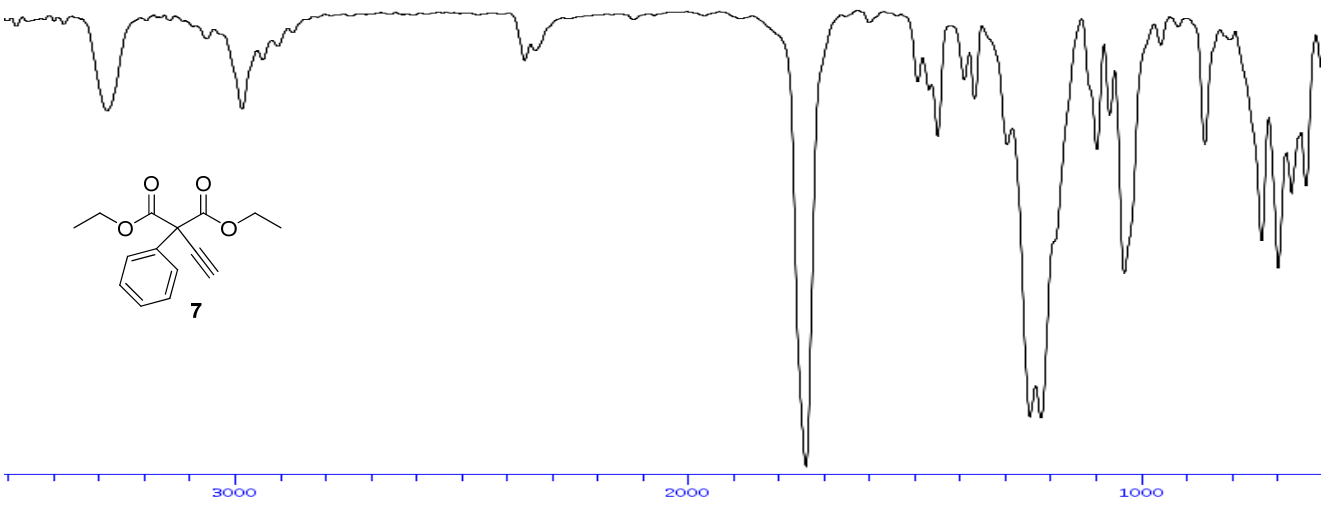
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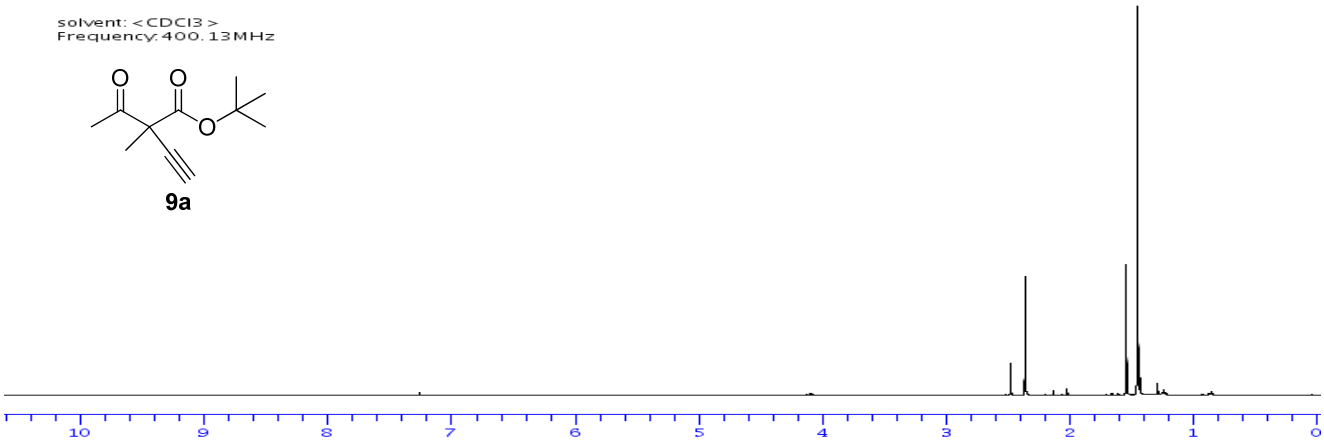
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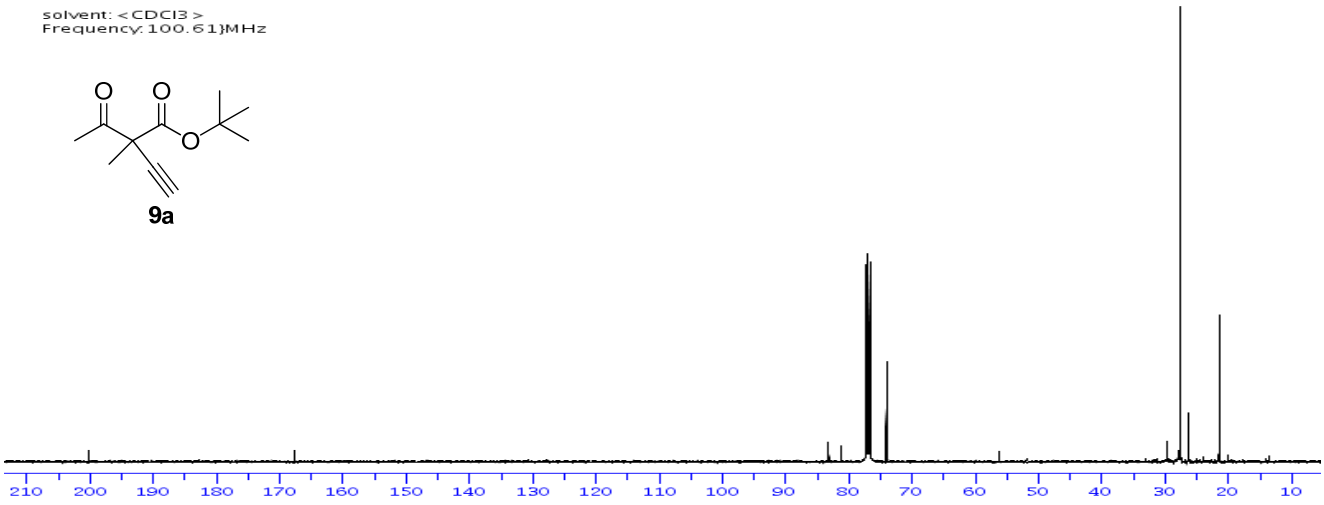
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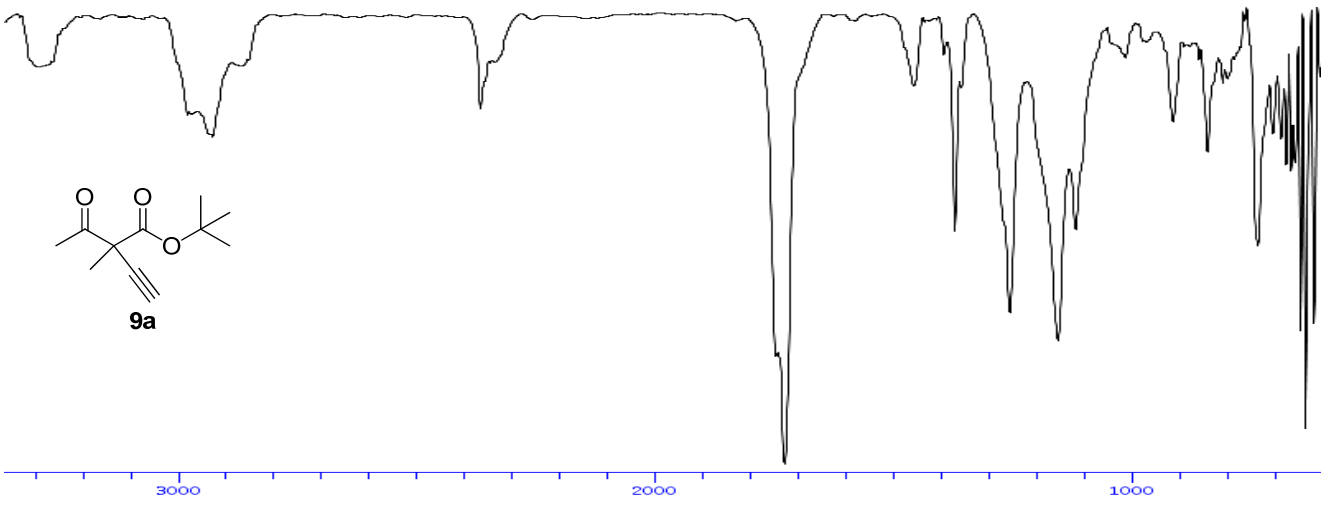
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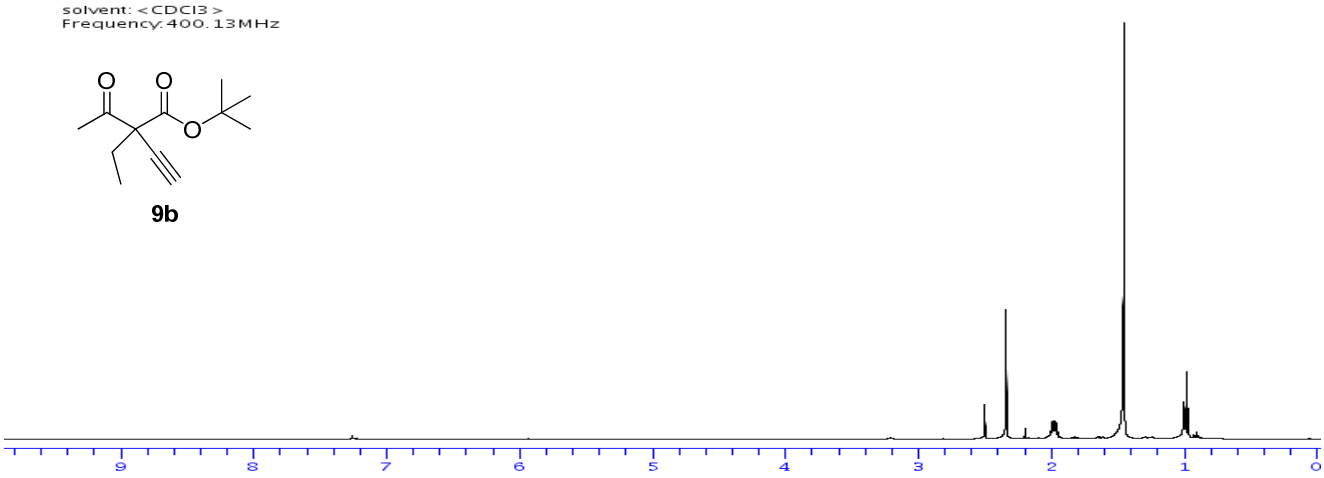
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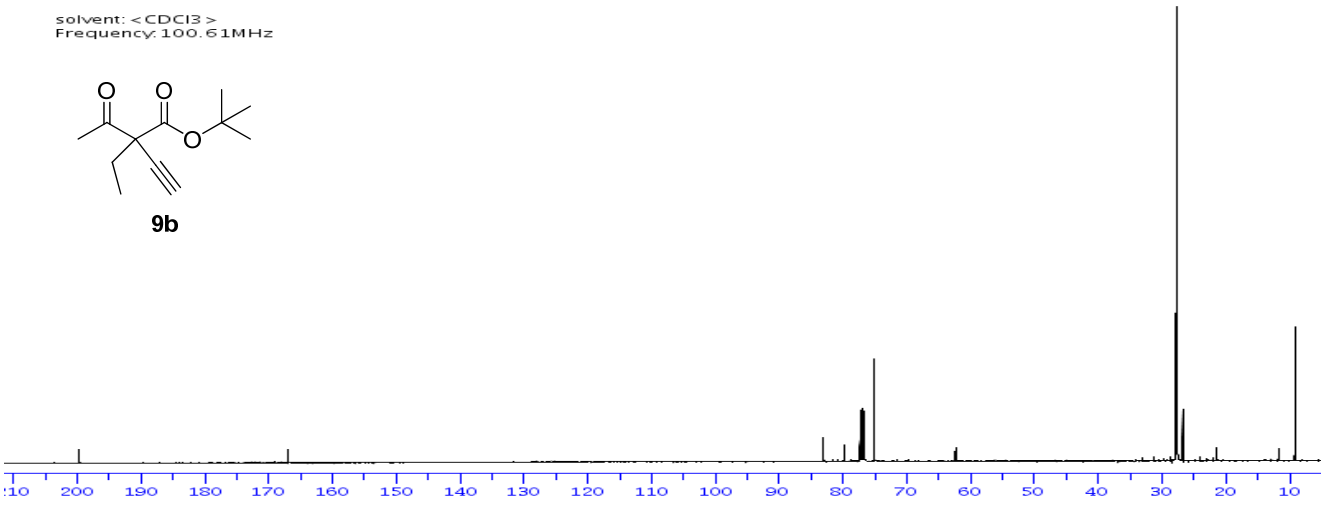
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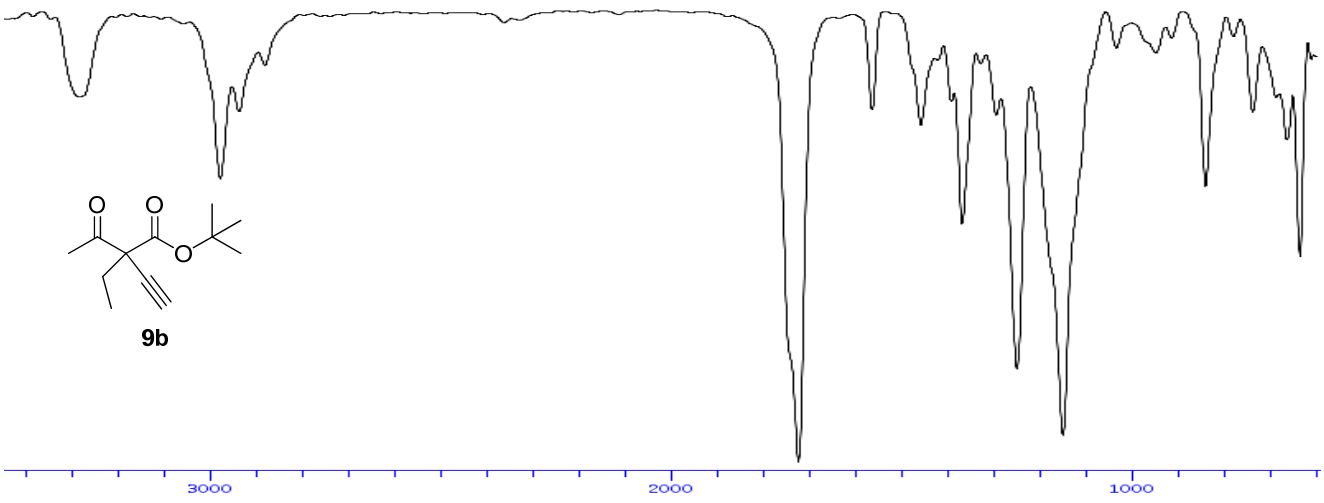
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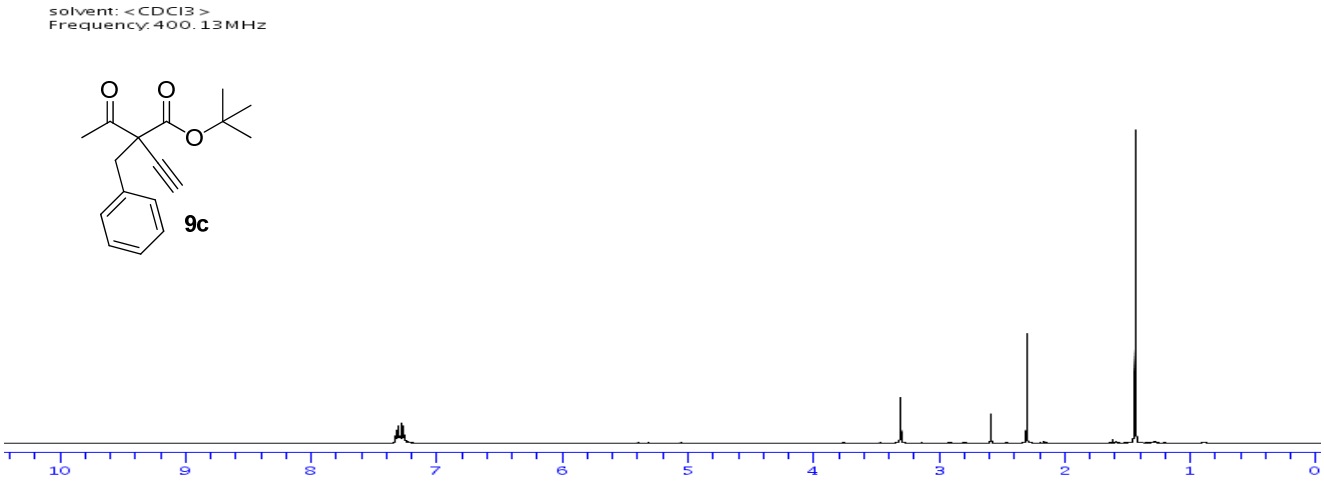
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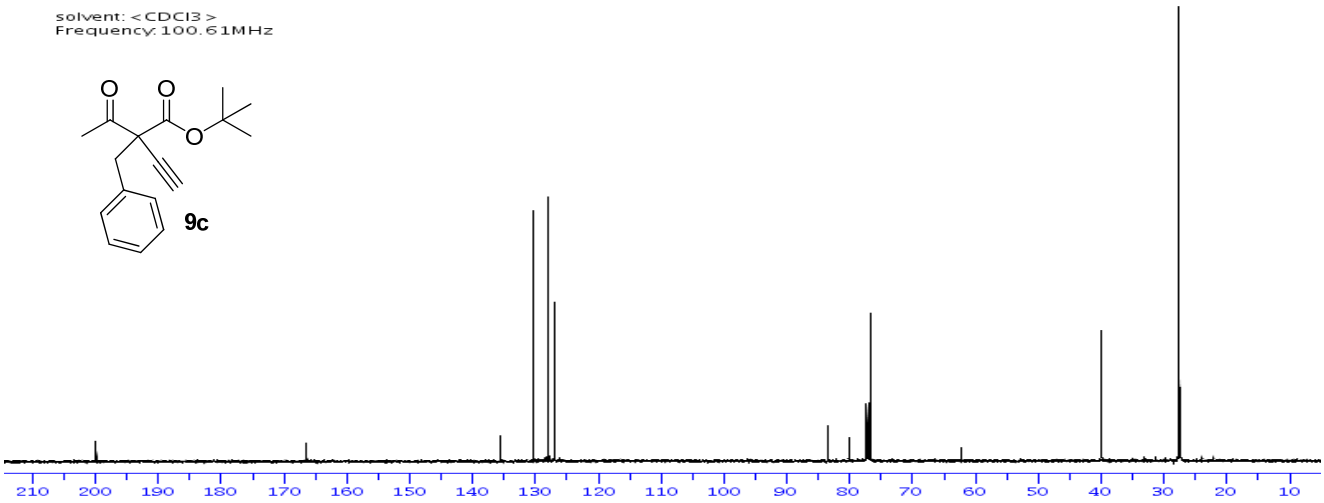
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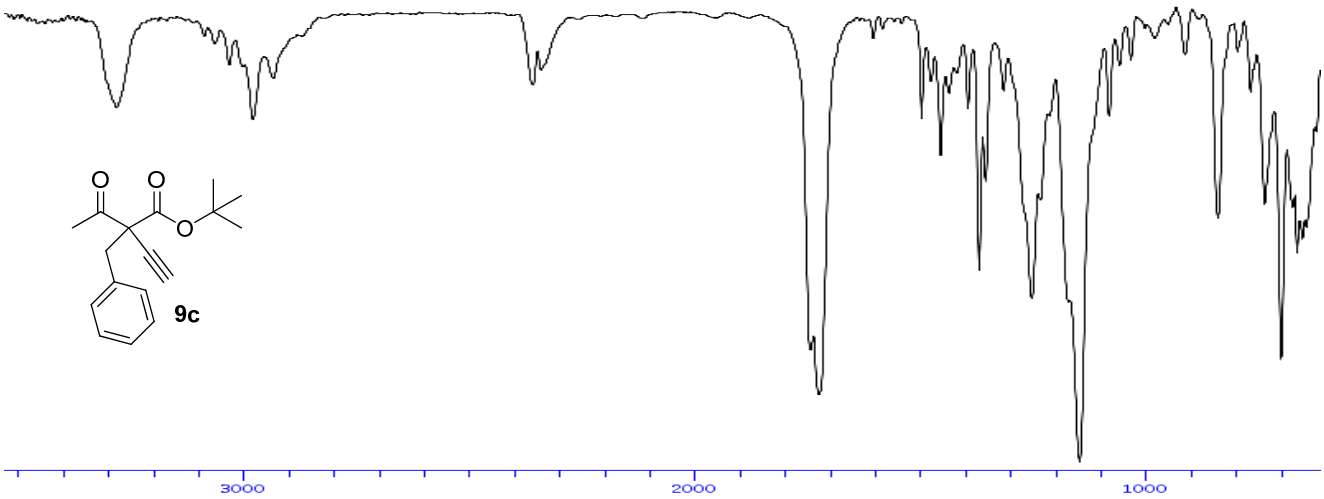
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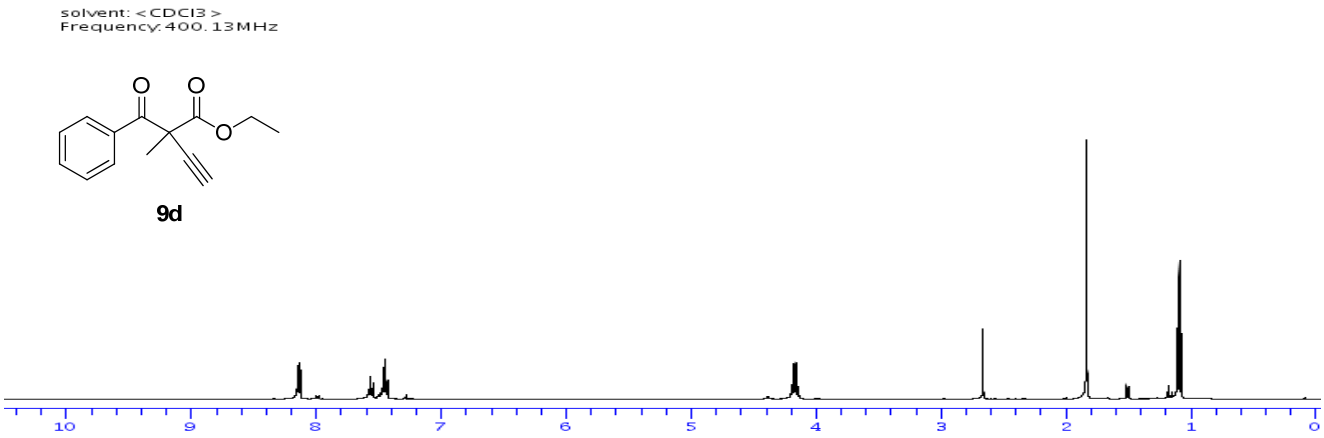
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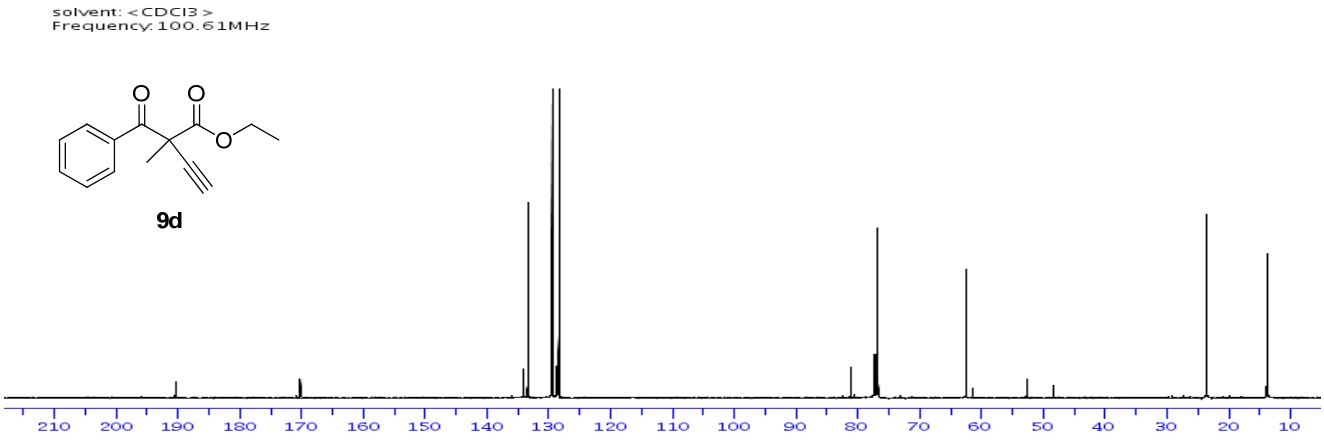
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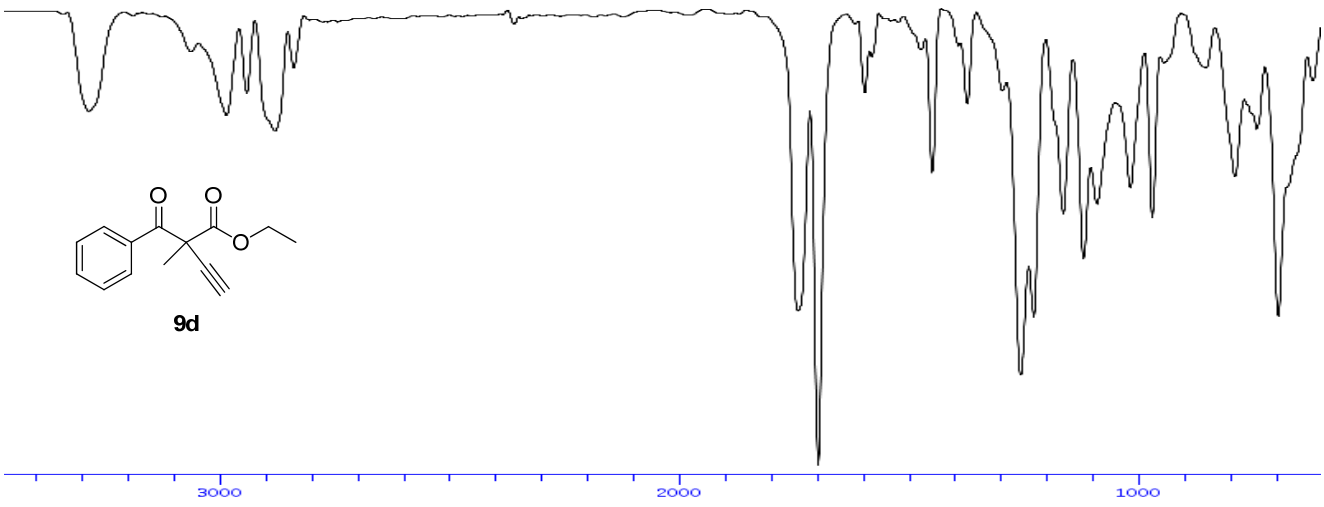
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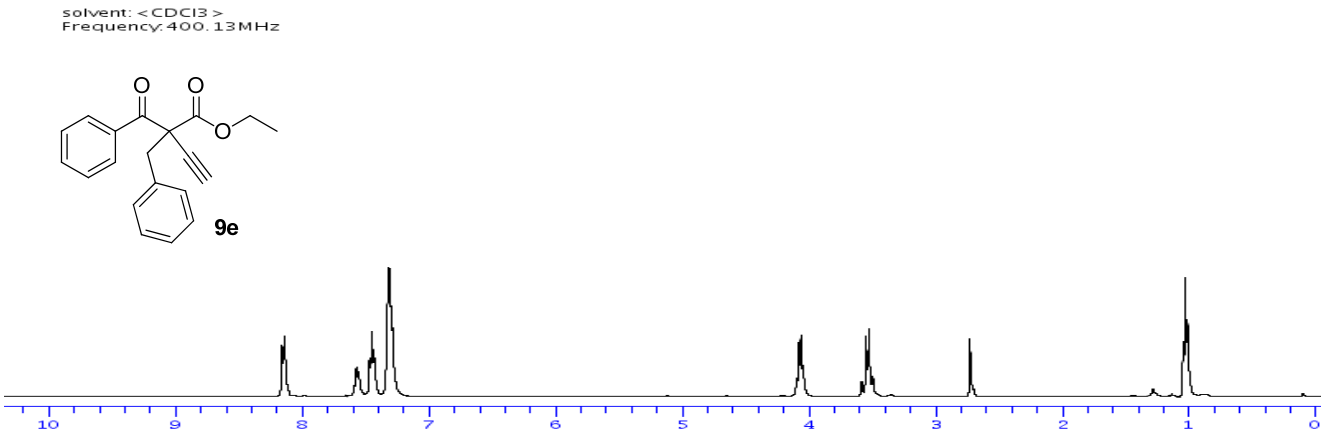
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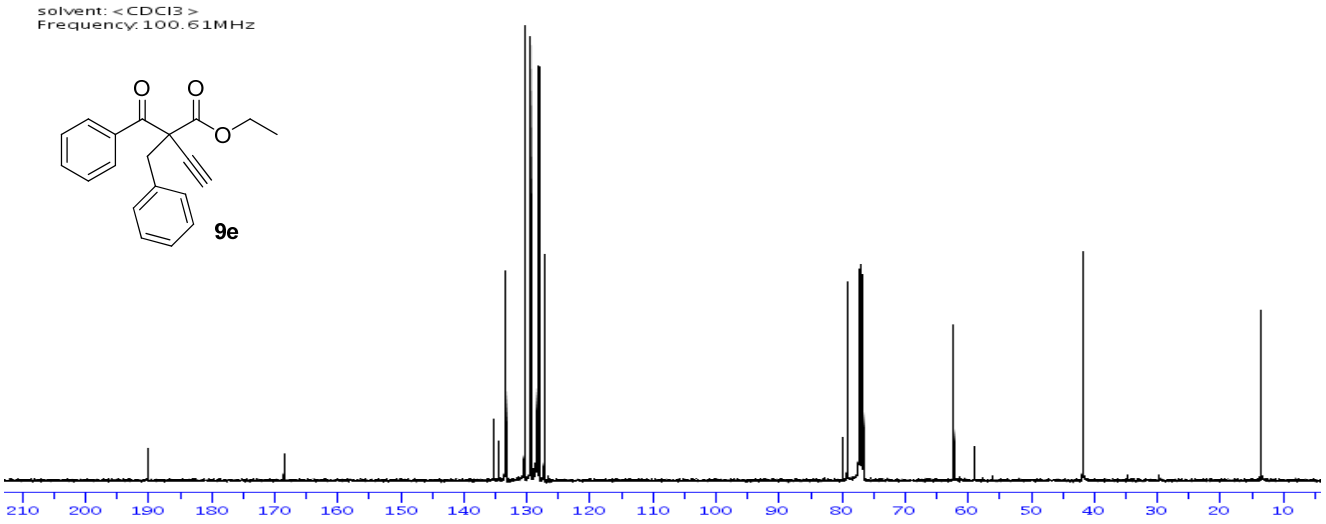
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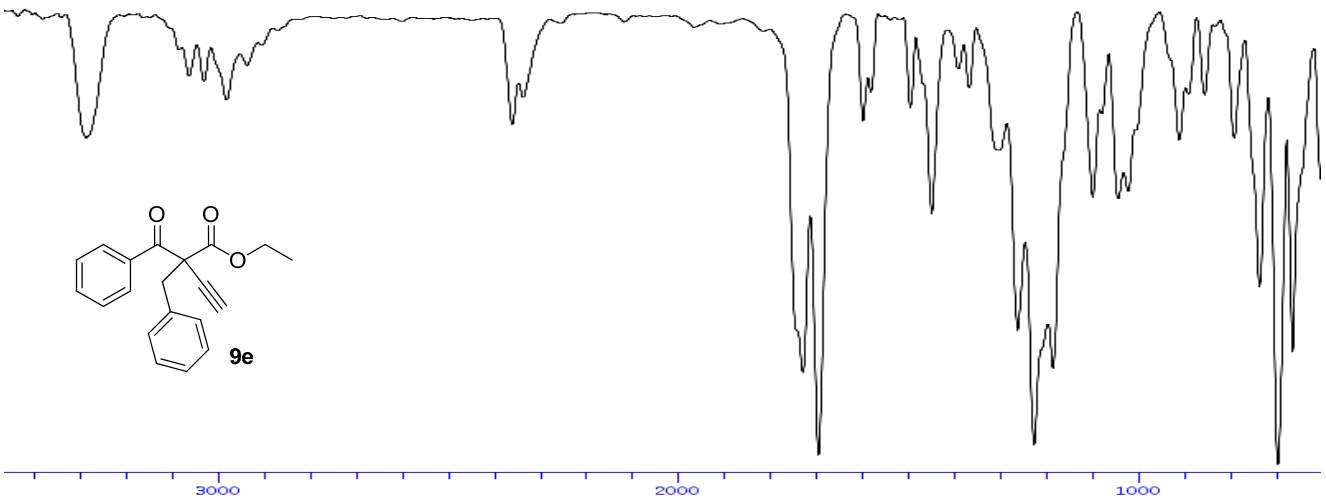
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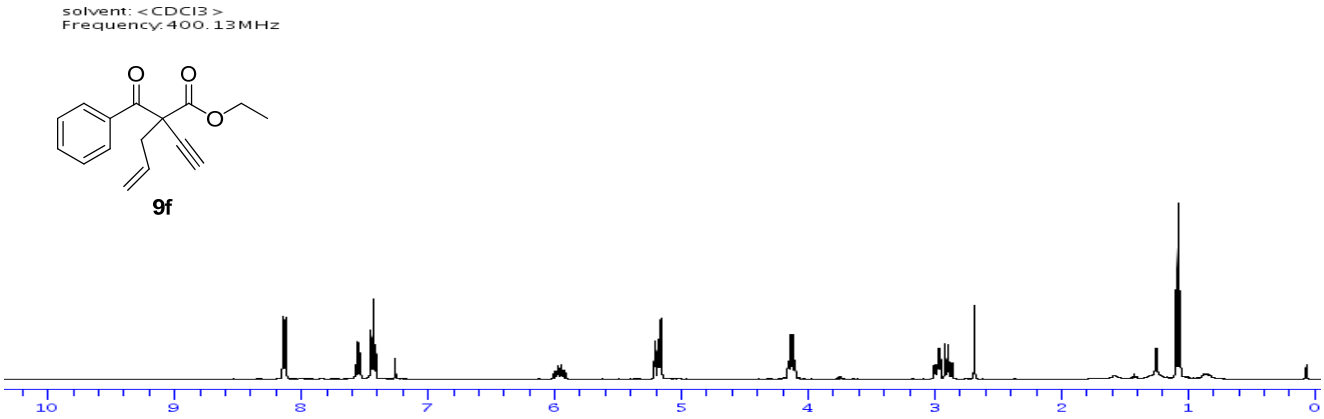
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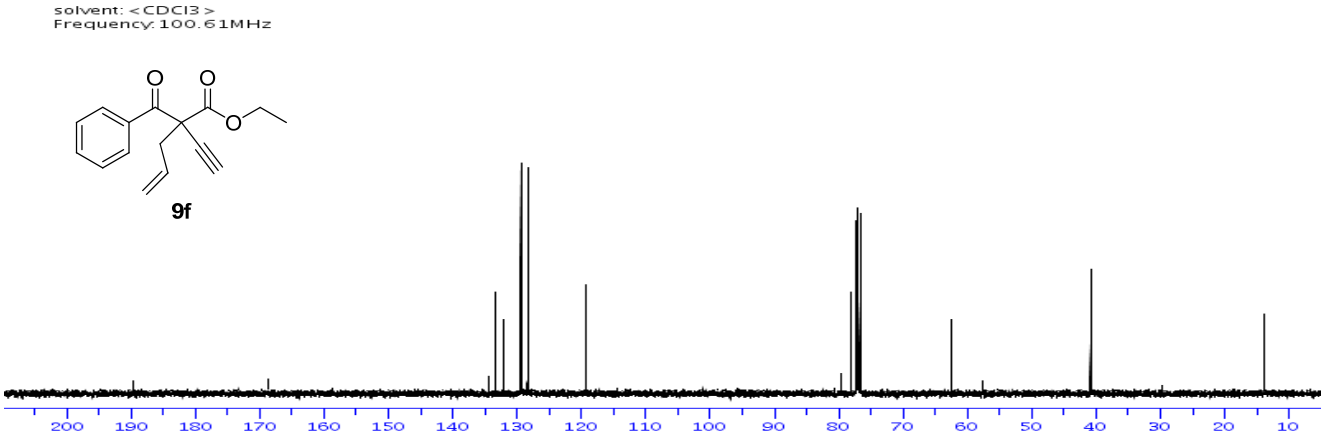
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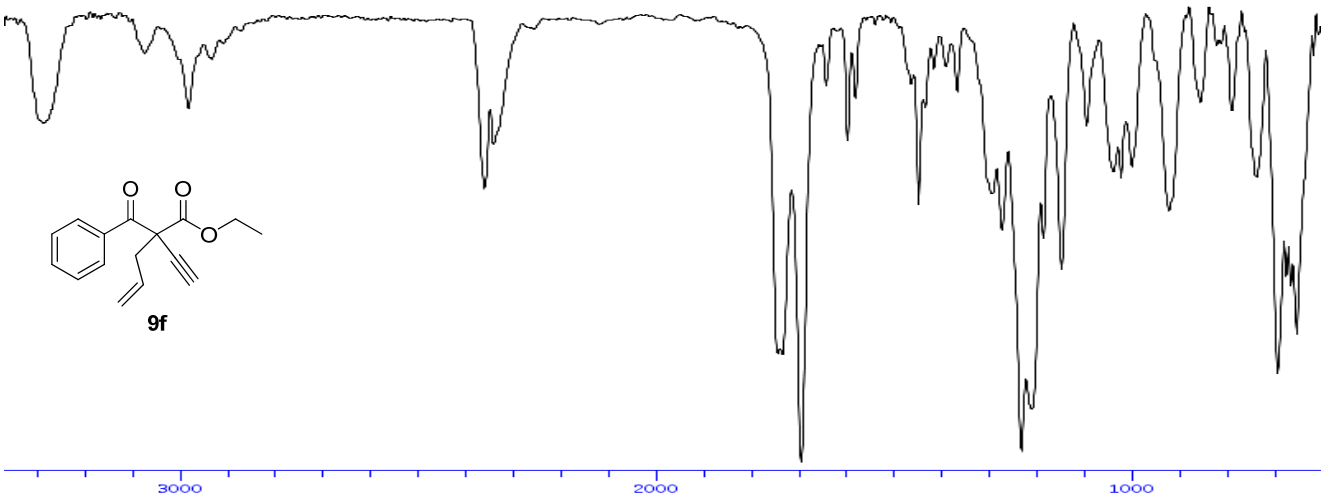
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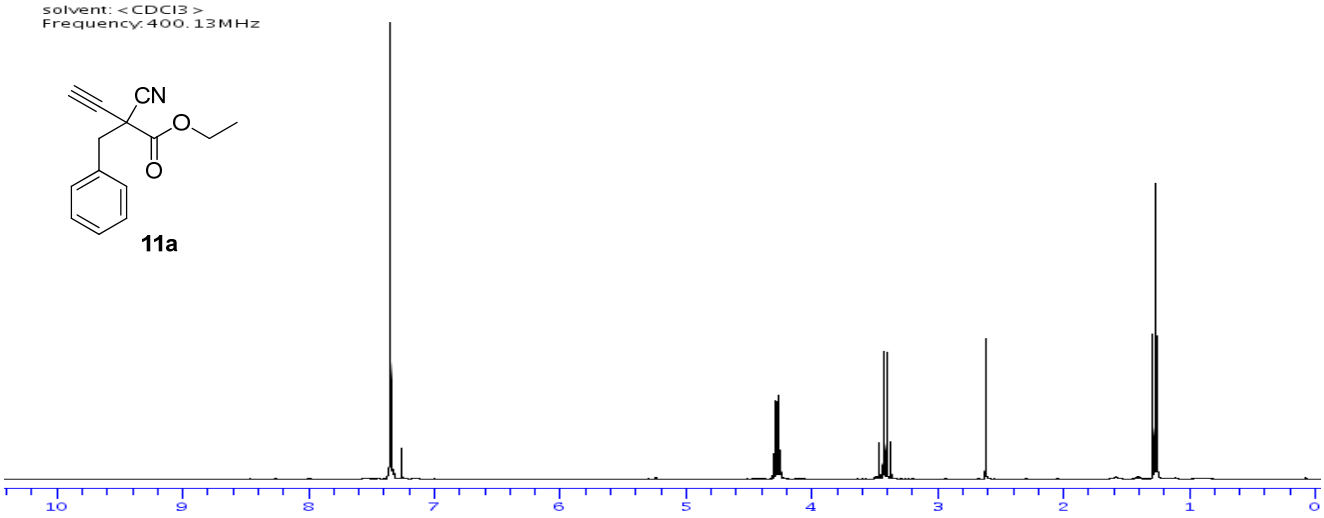
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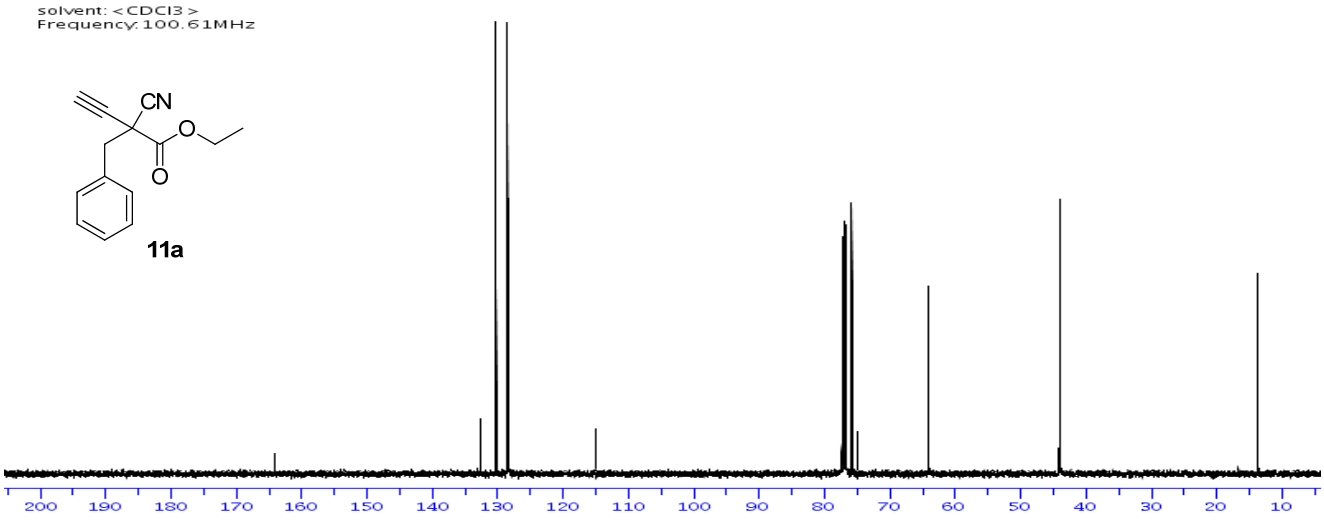
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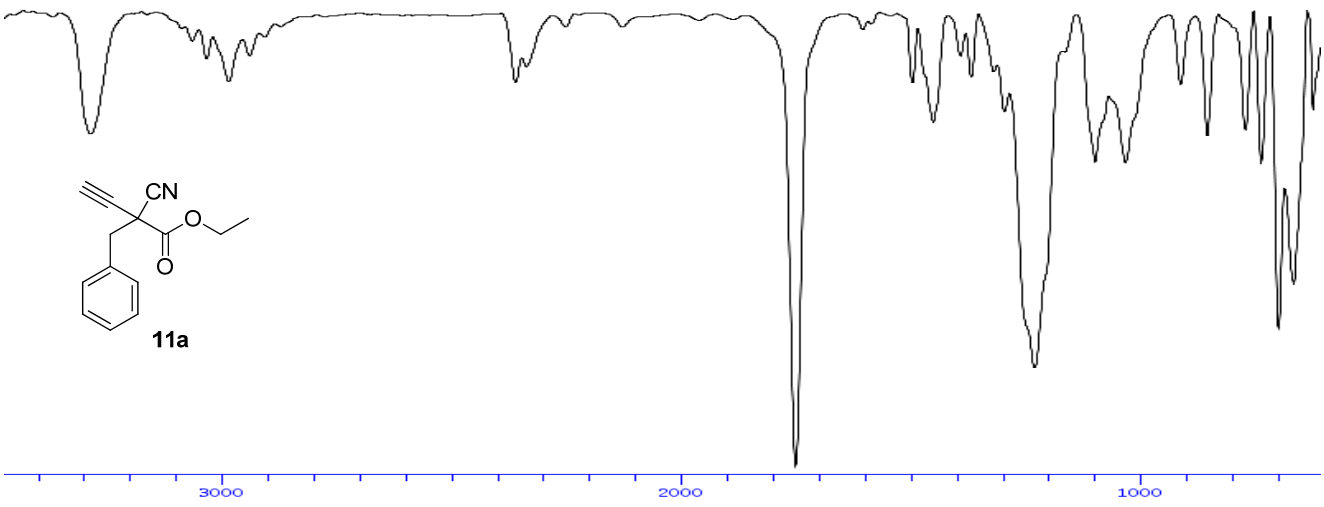
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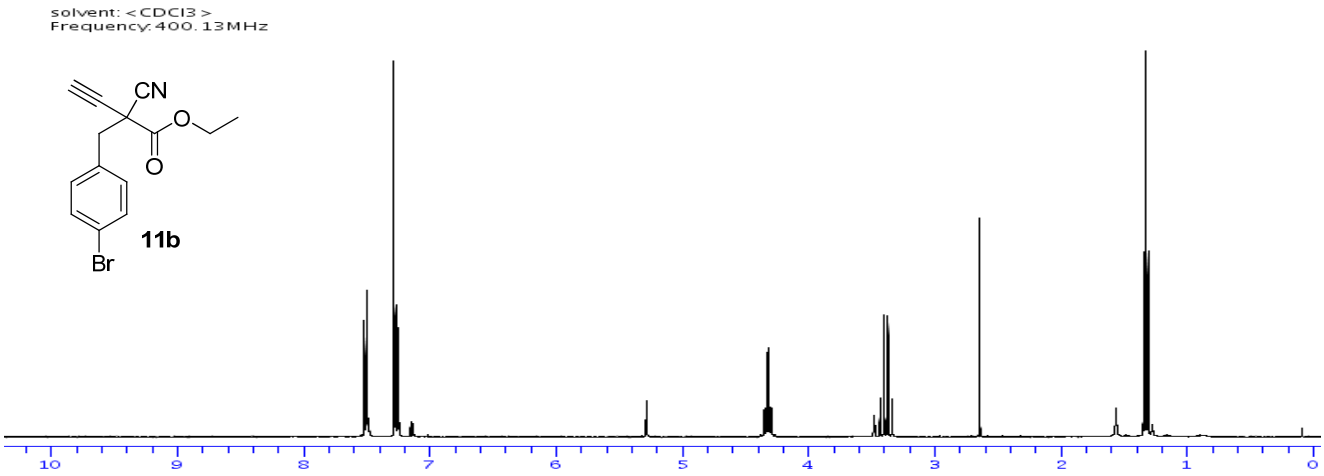
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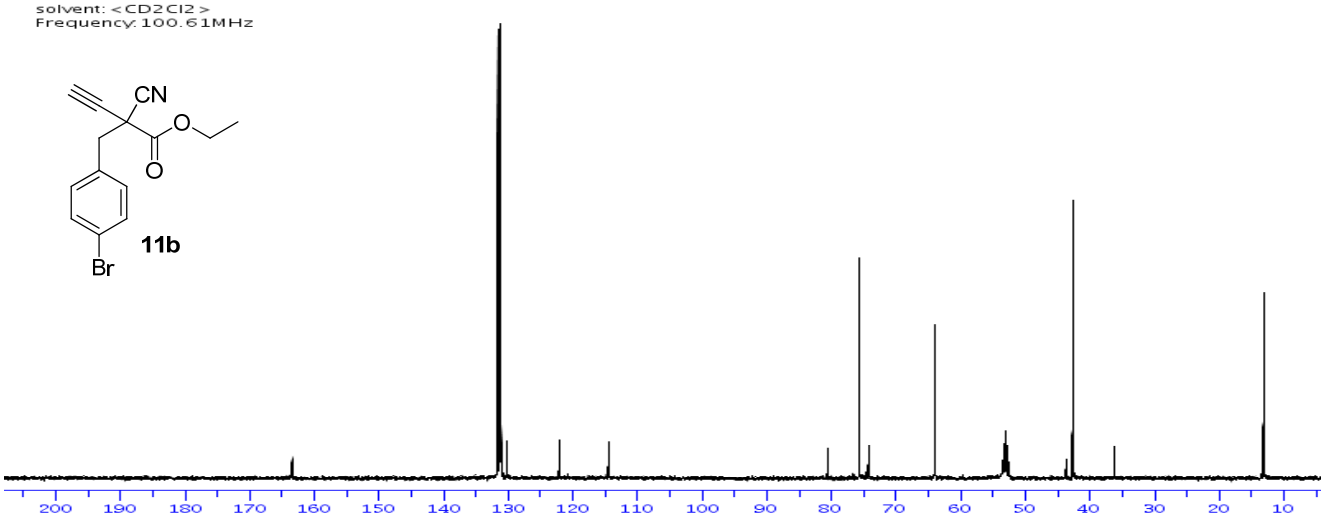
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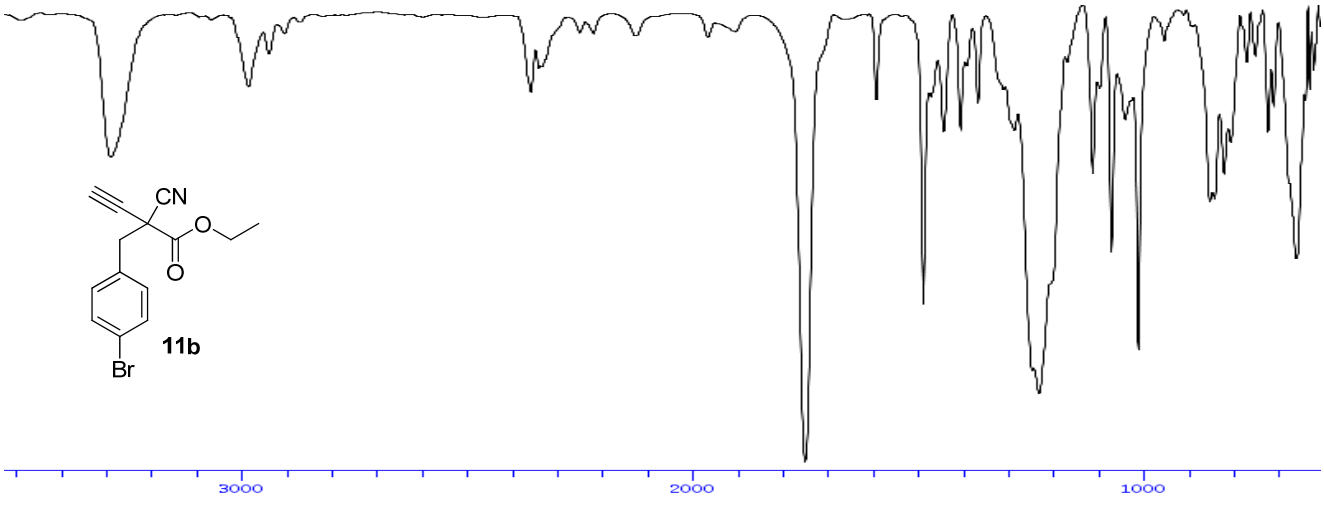
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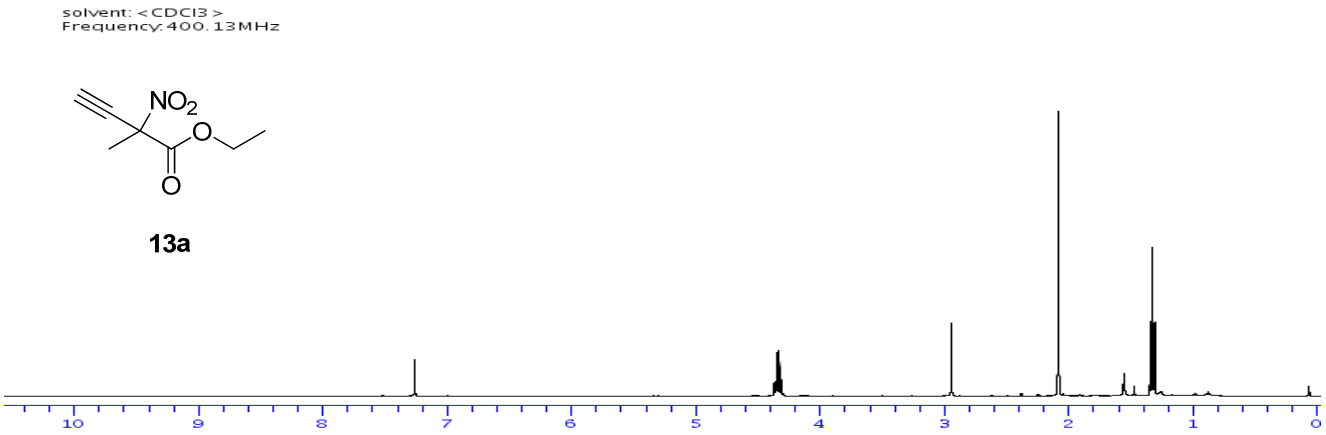
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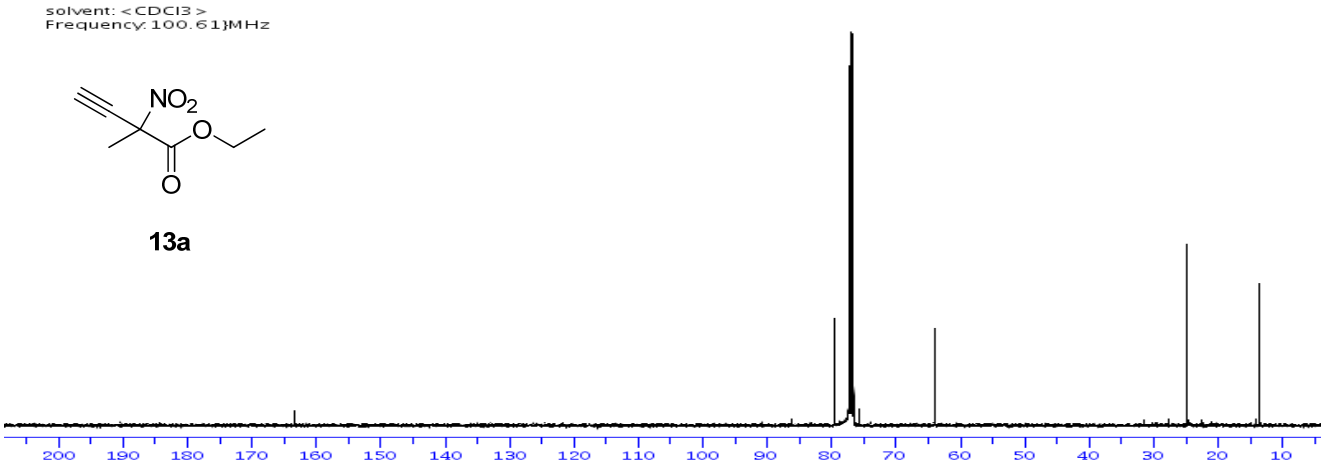
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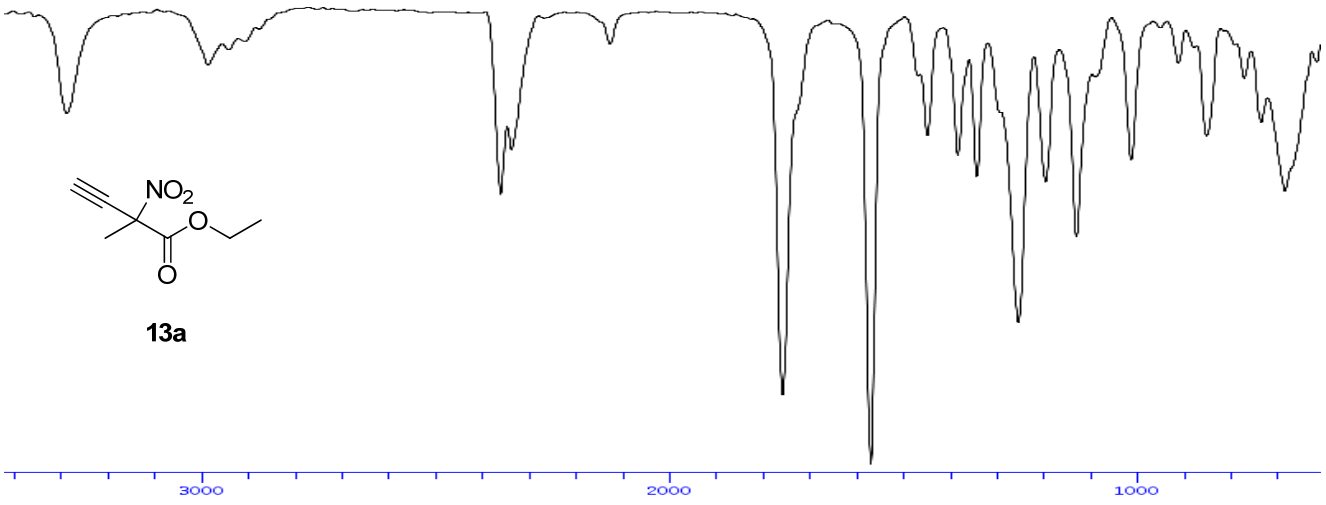
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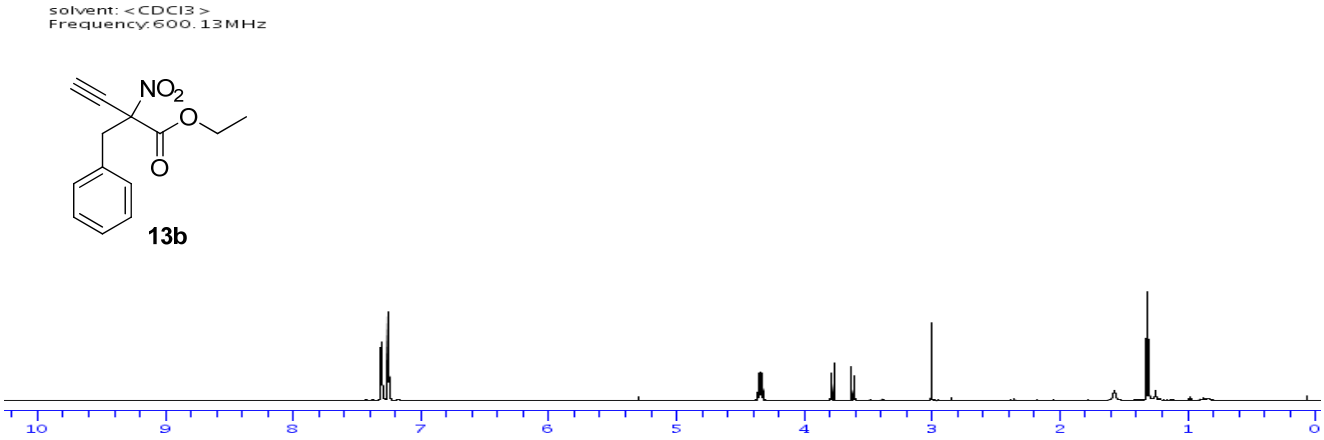
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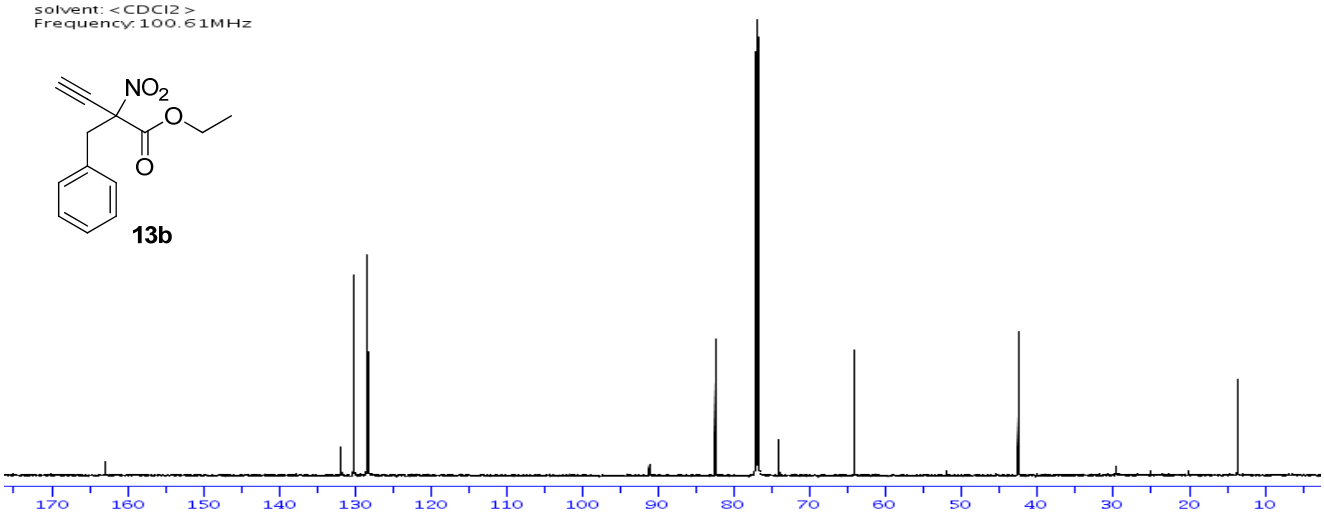
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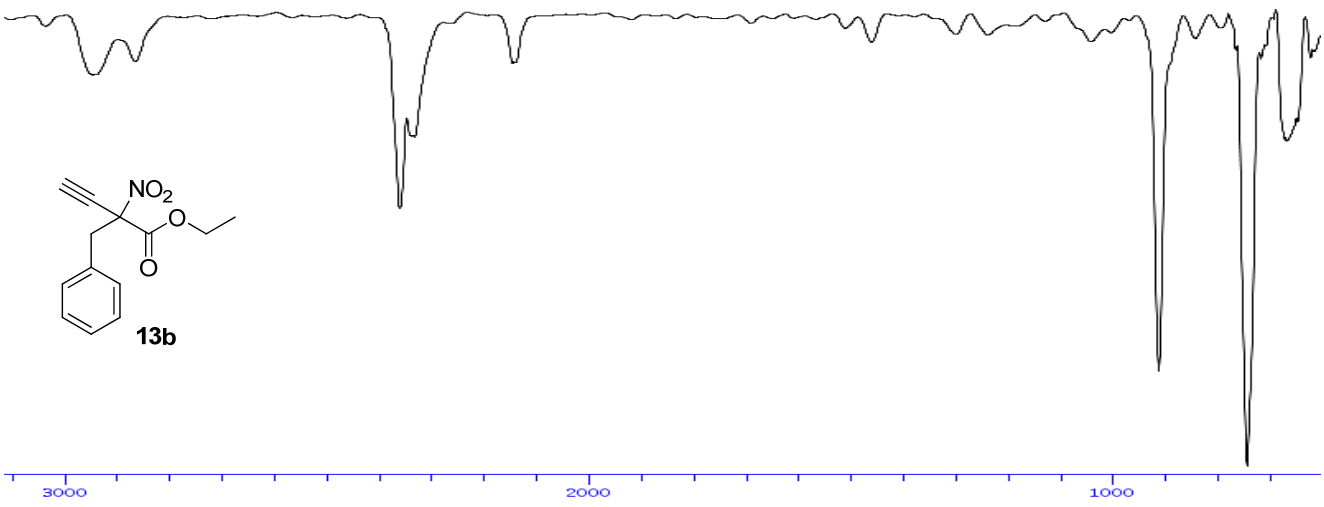
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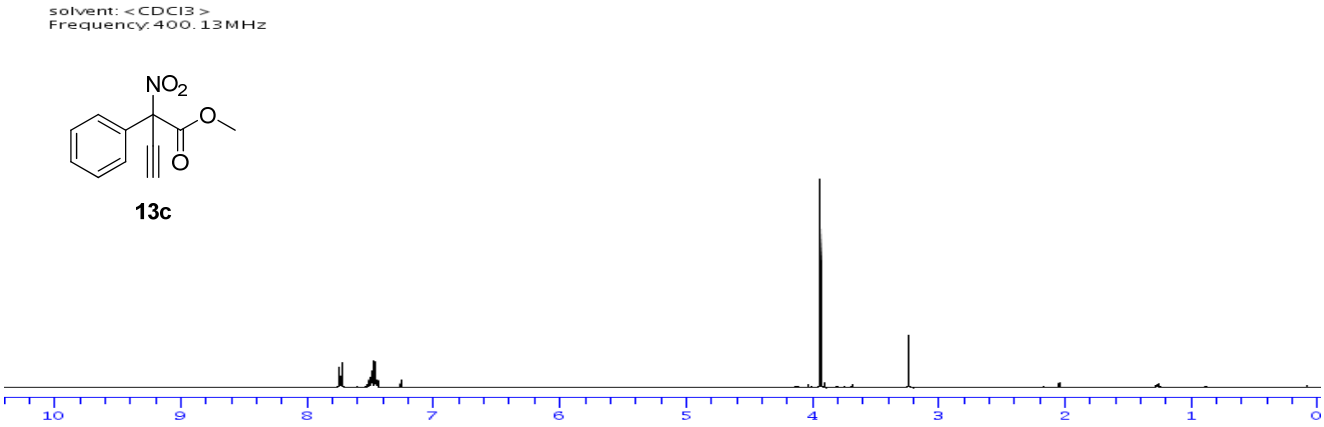
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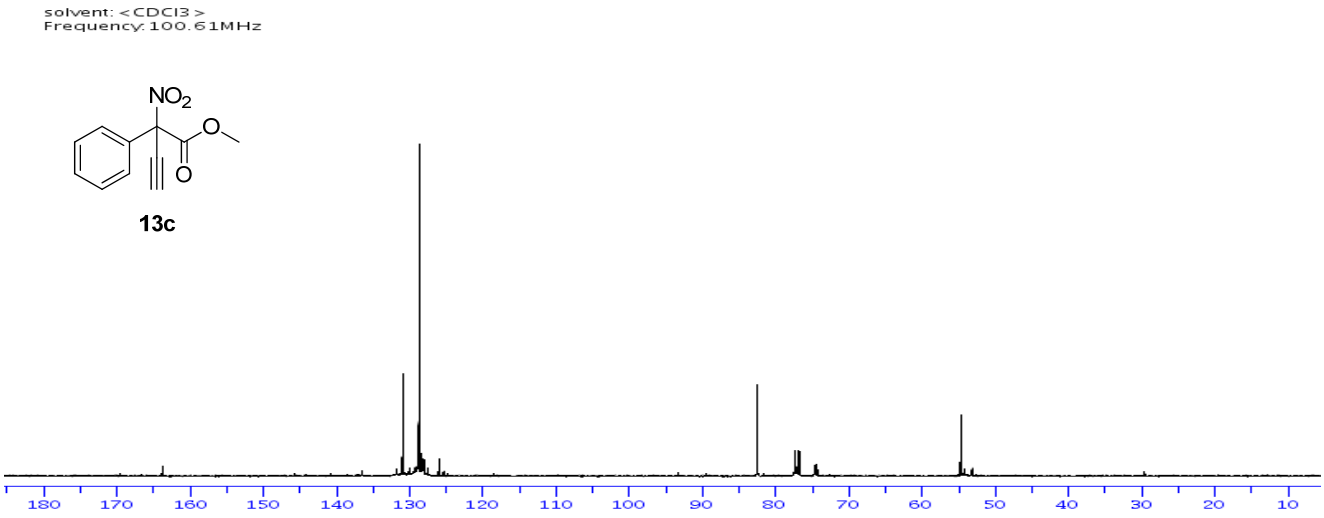
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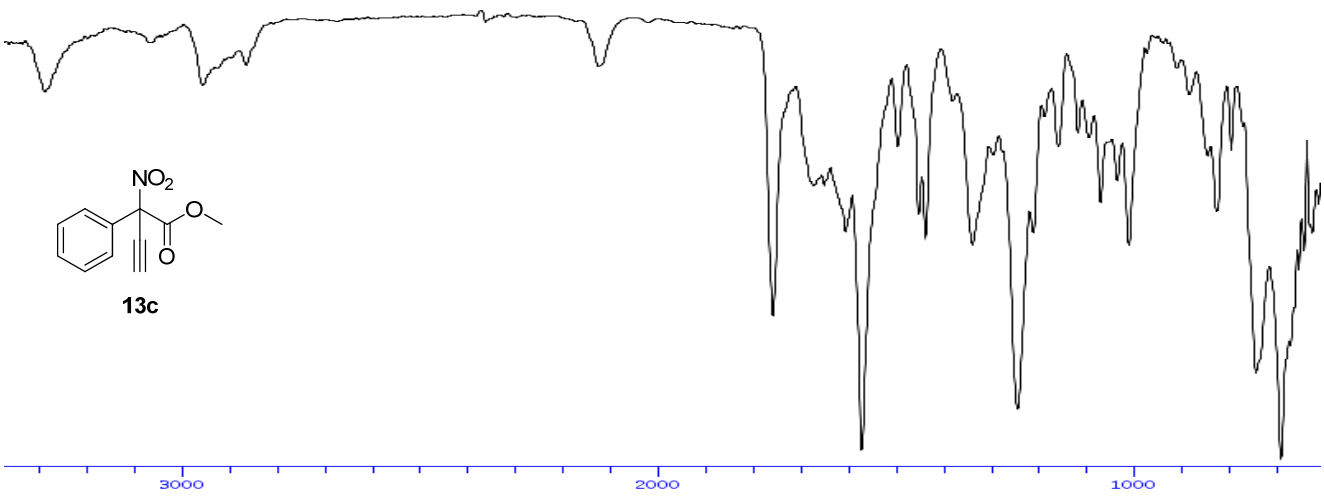
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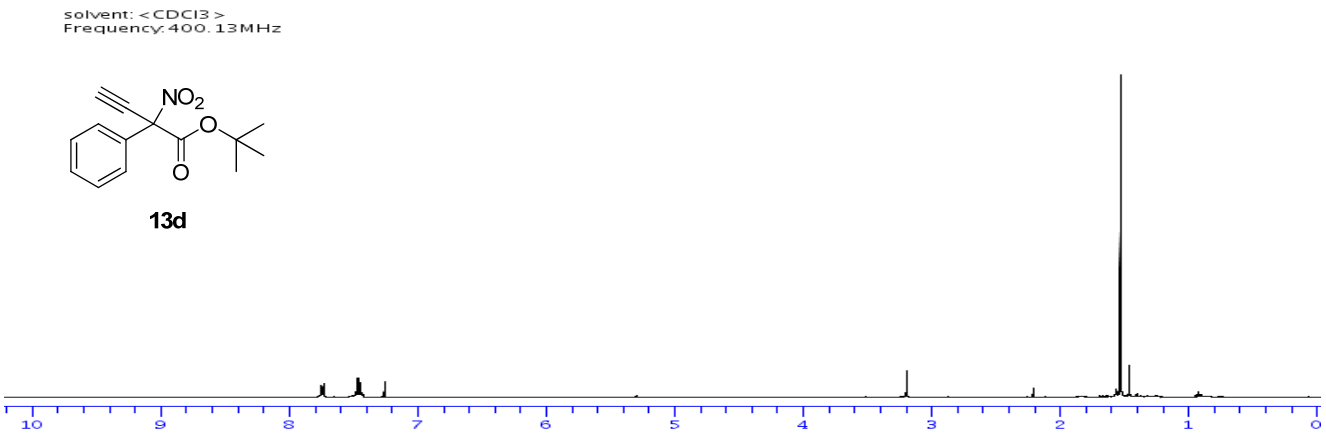
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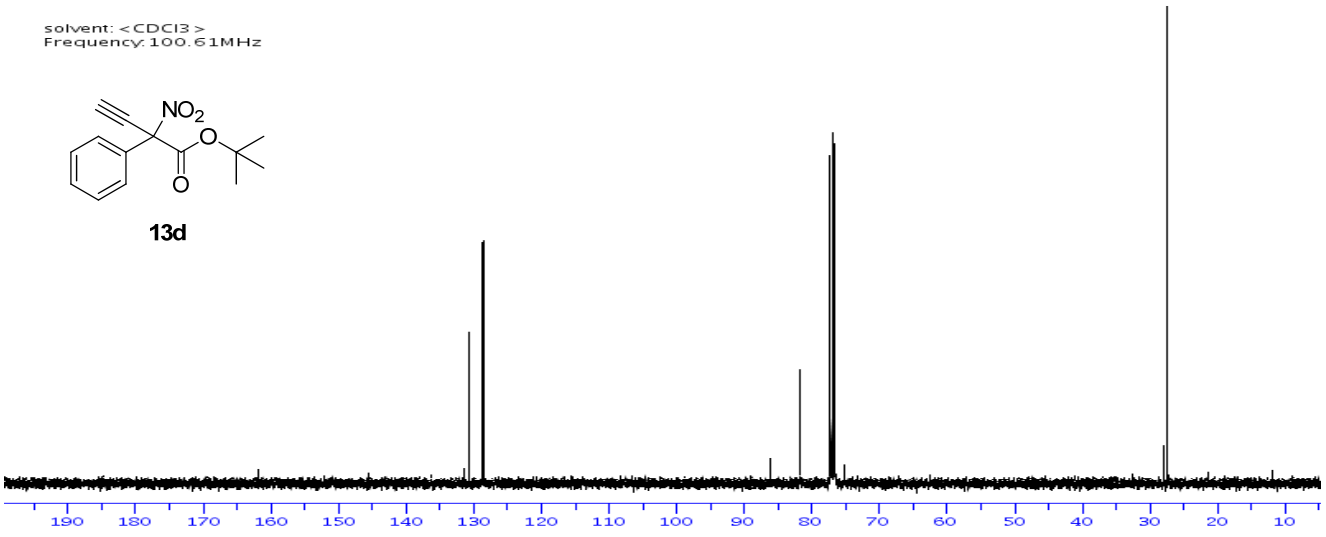
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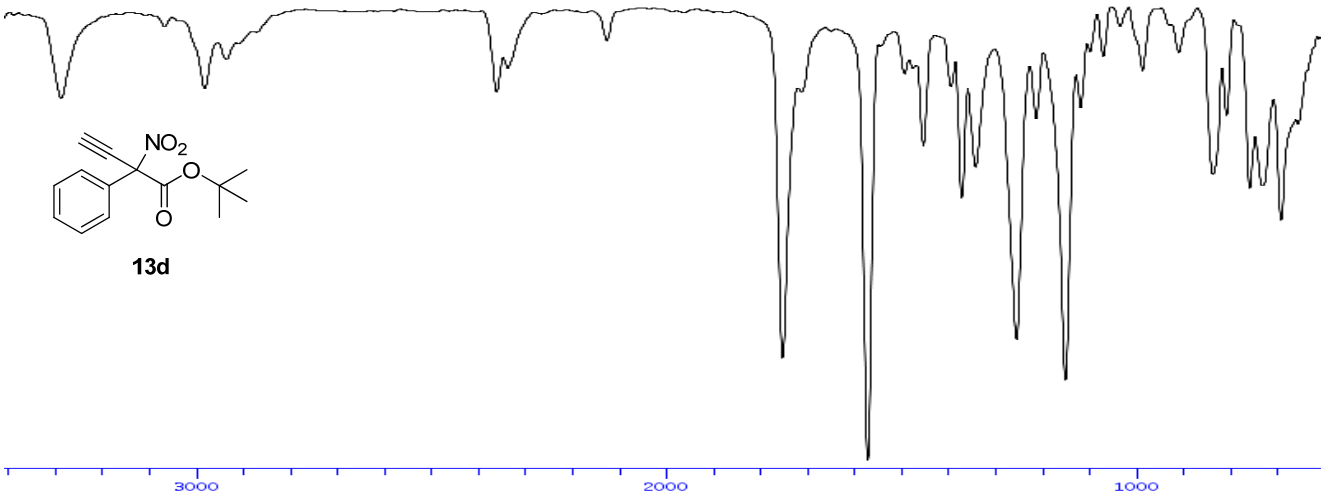
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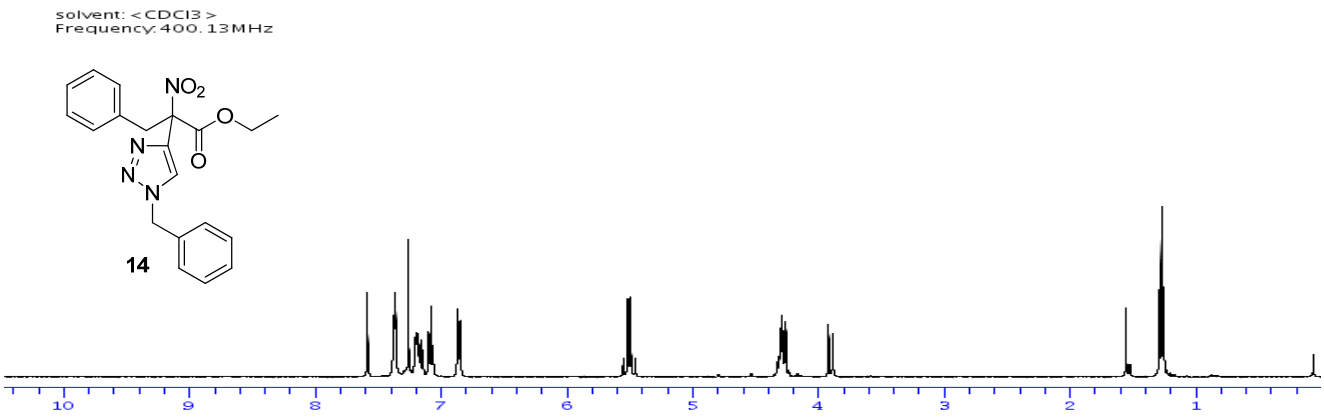
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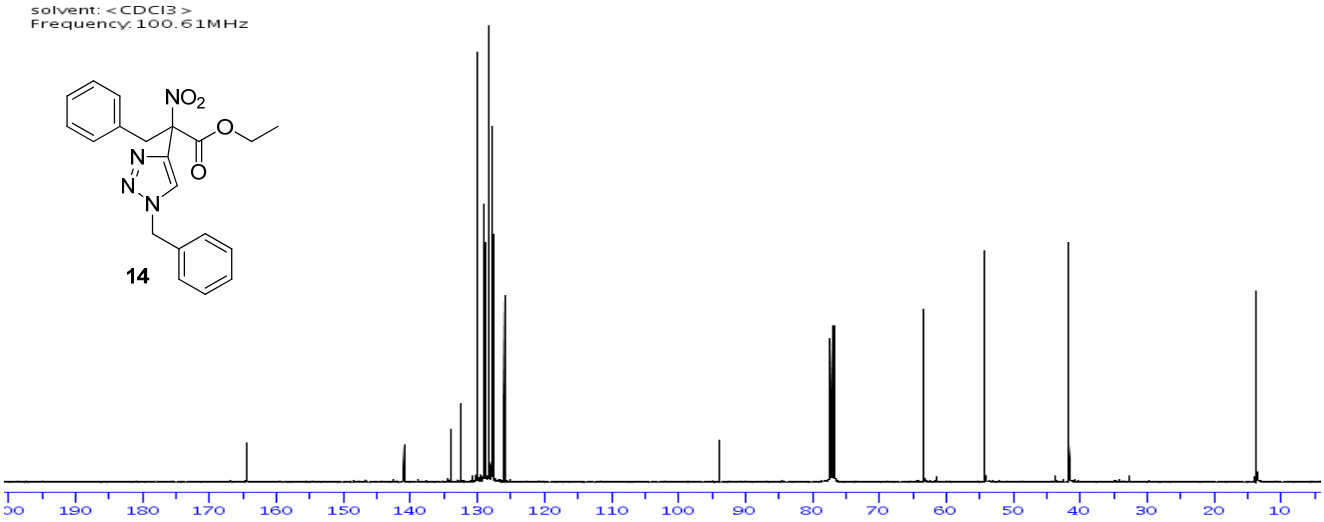
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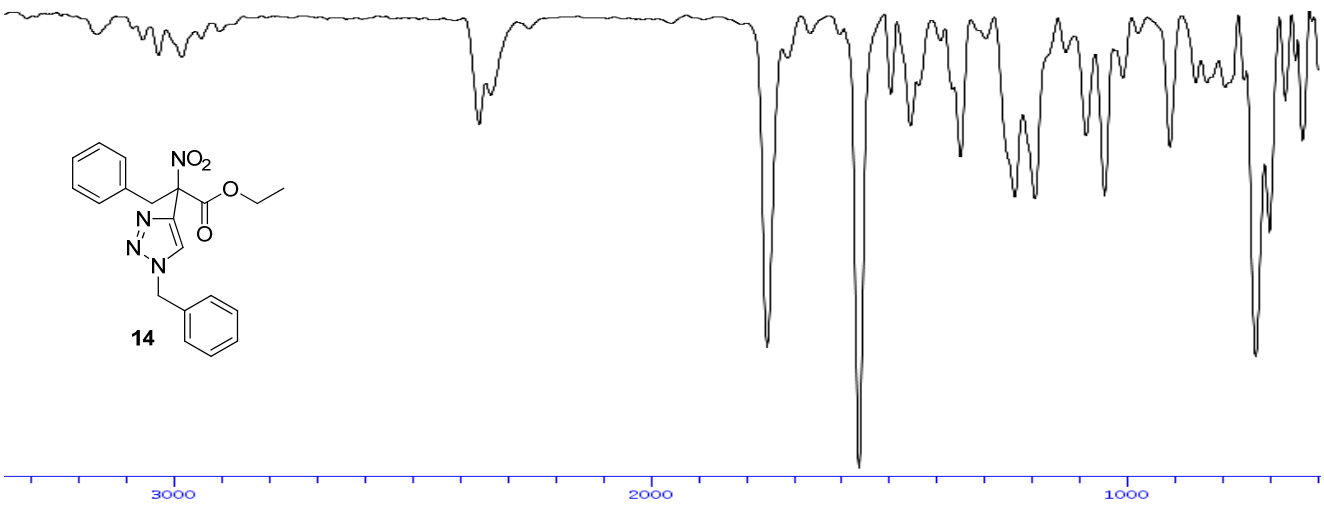
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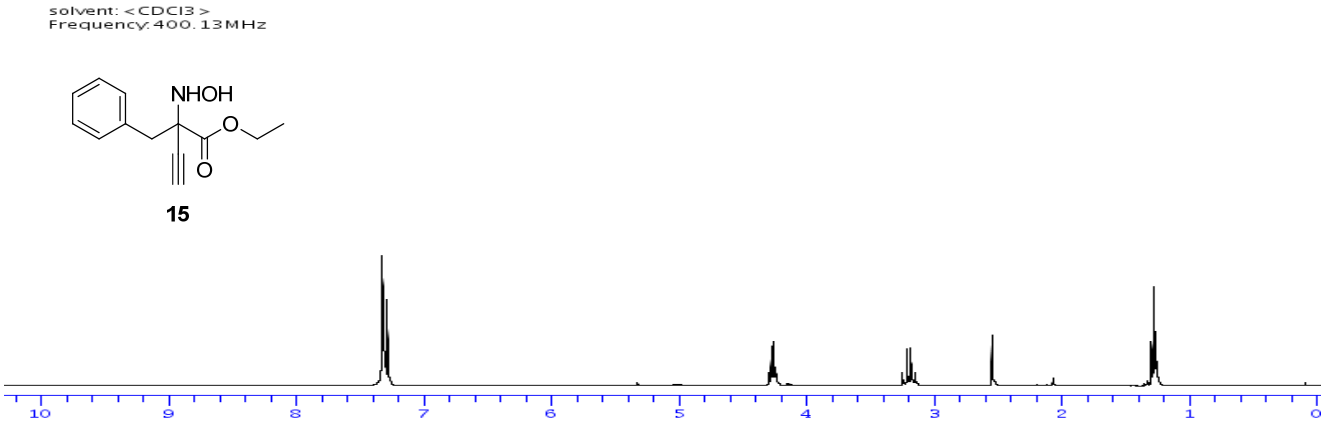
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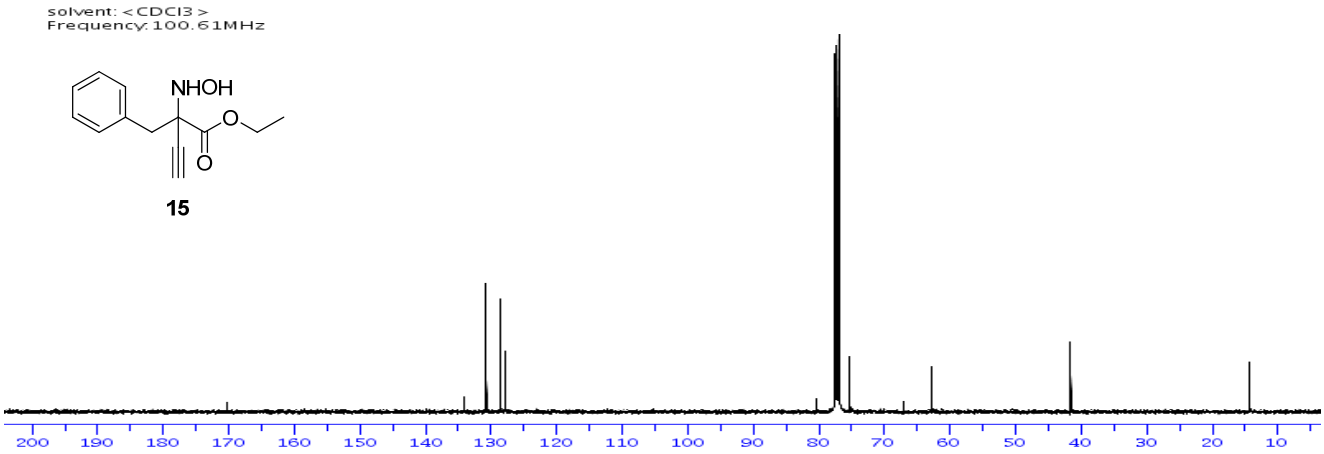
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NHOH
O
O
15
200
190
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150
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120
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100
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80
70
60
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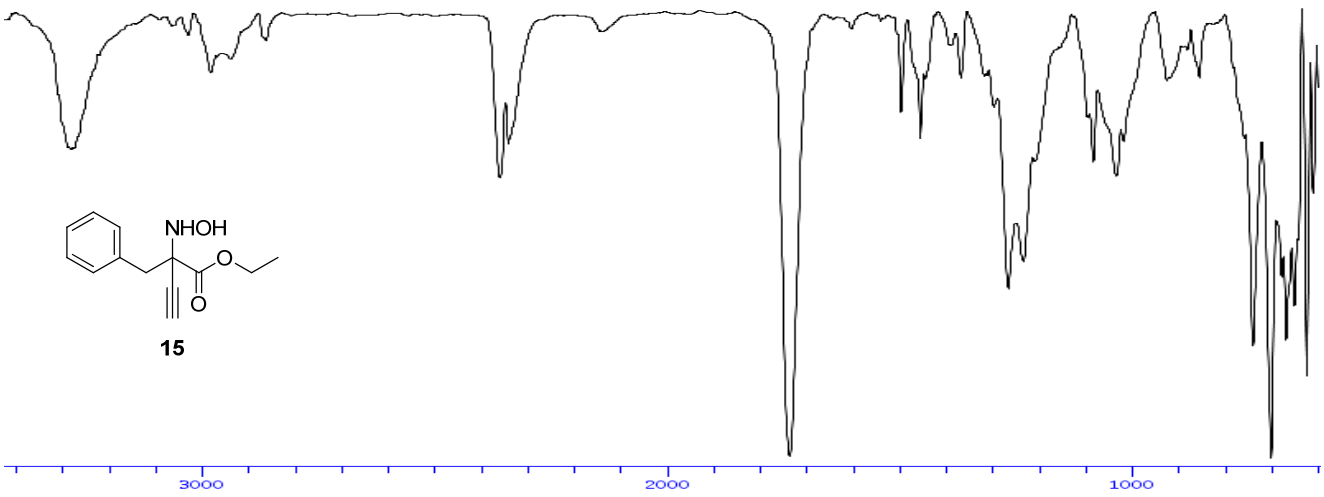
40
30
20
10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2000
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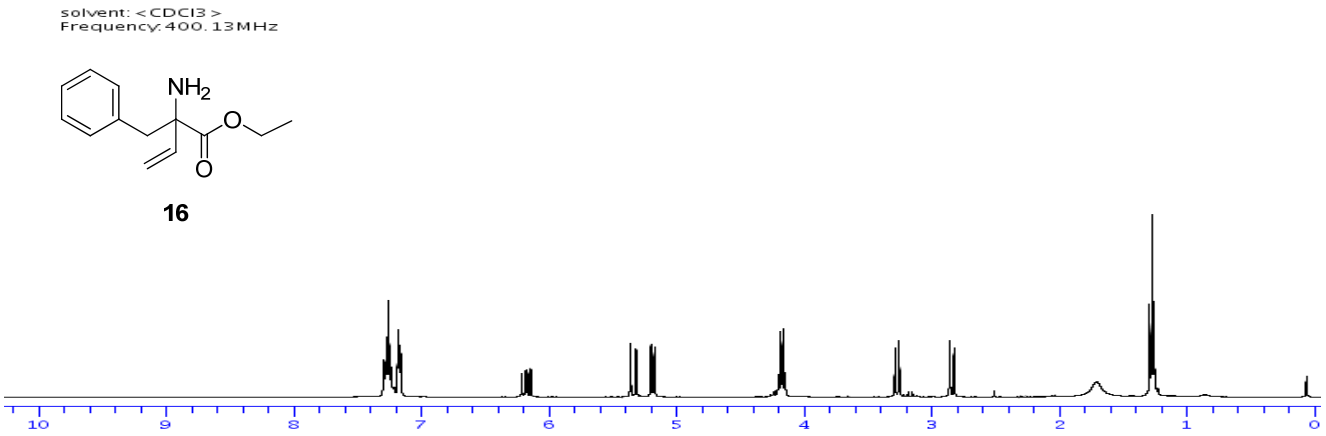
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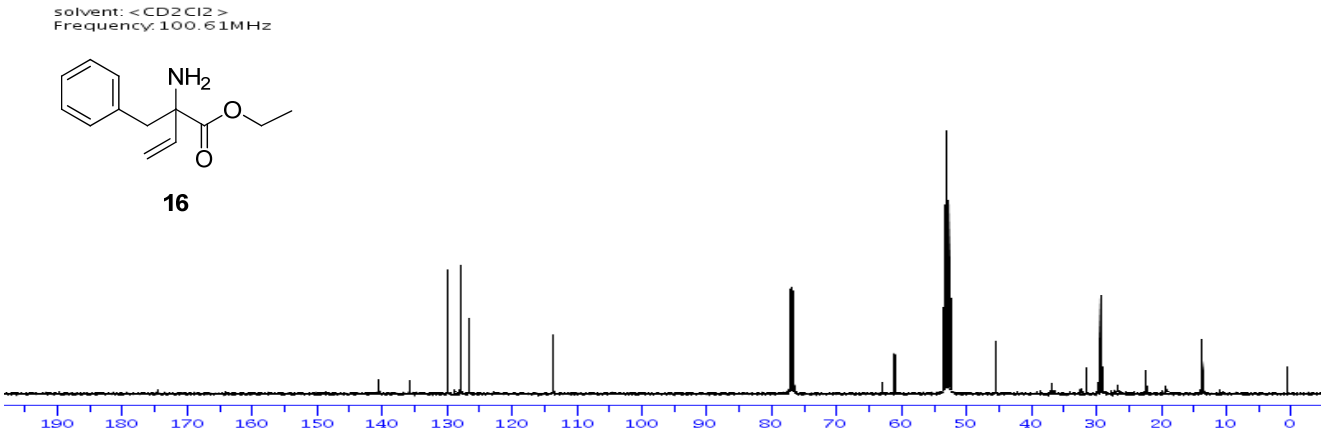
O
16
10
9
8
7
6
5
4
3
2
1
0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NH2
O
O
16
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180
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70
60
50
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30
20
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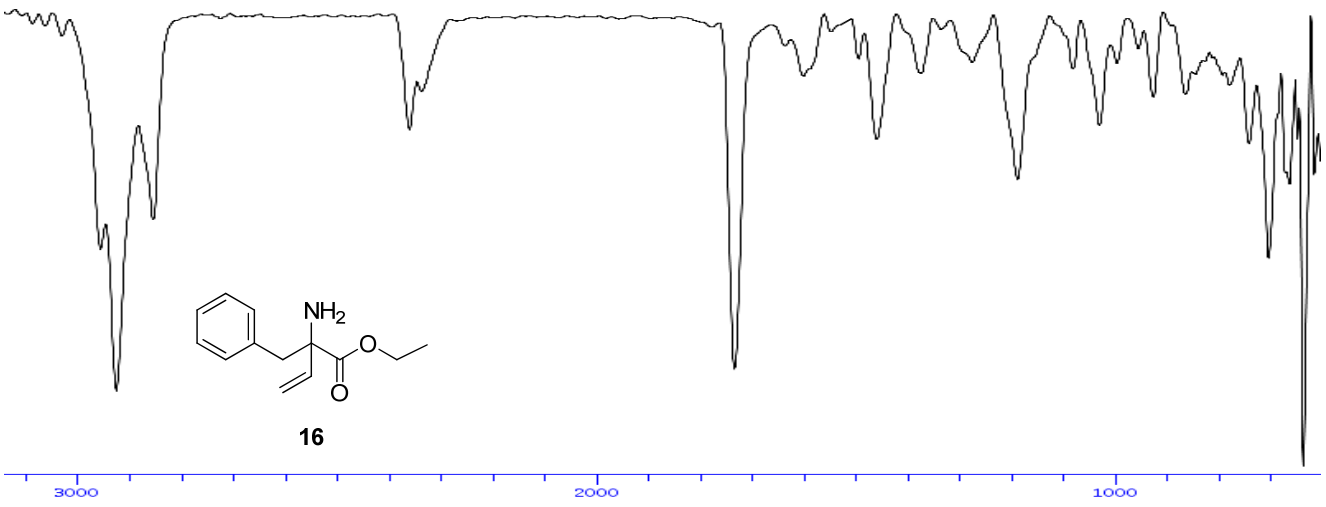
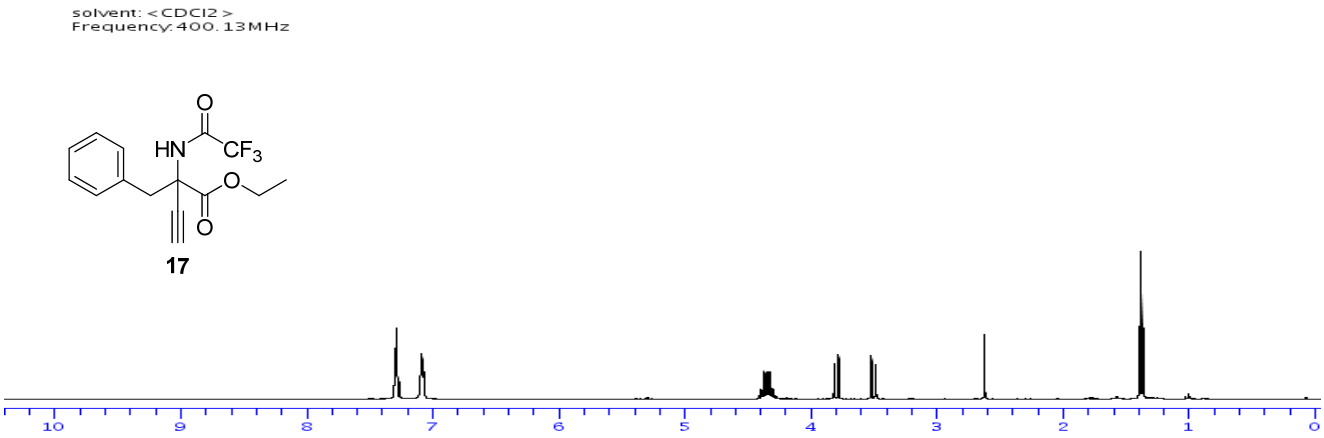
0


NH2
O
O
16
3000
2000
1000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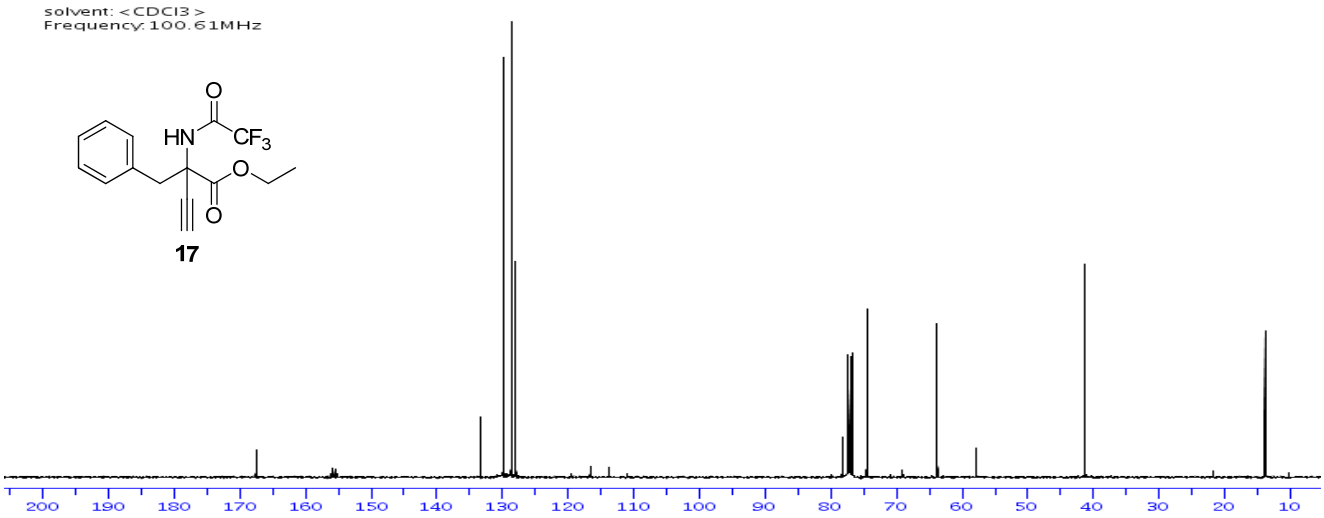
CF3
O
O
O
17
10
9
8
7
6
5
4
3
2
1
0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CF3
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O
O
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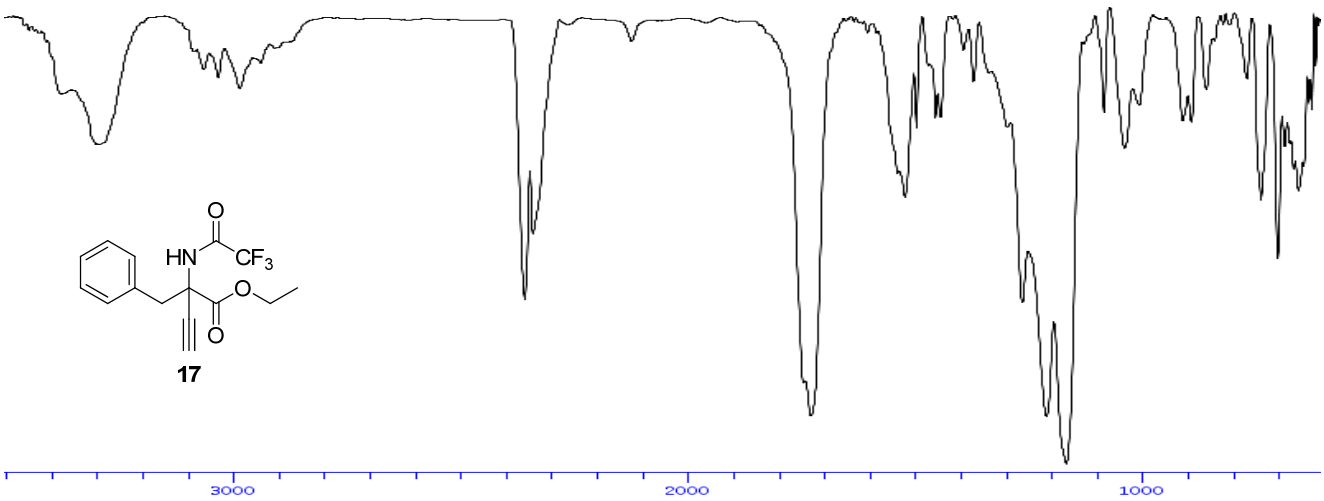
HN
CF3
O
O
O
17
3000
2000
1000

solvent: <CDCl3>
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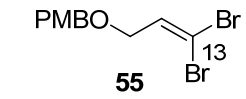

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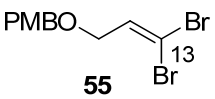

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solvent: <CDCl3>
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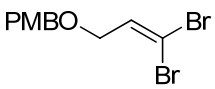
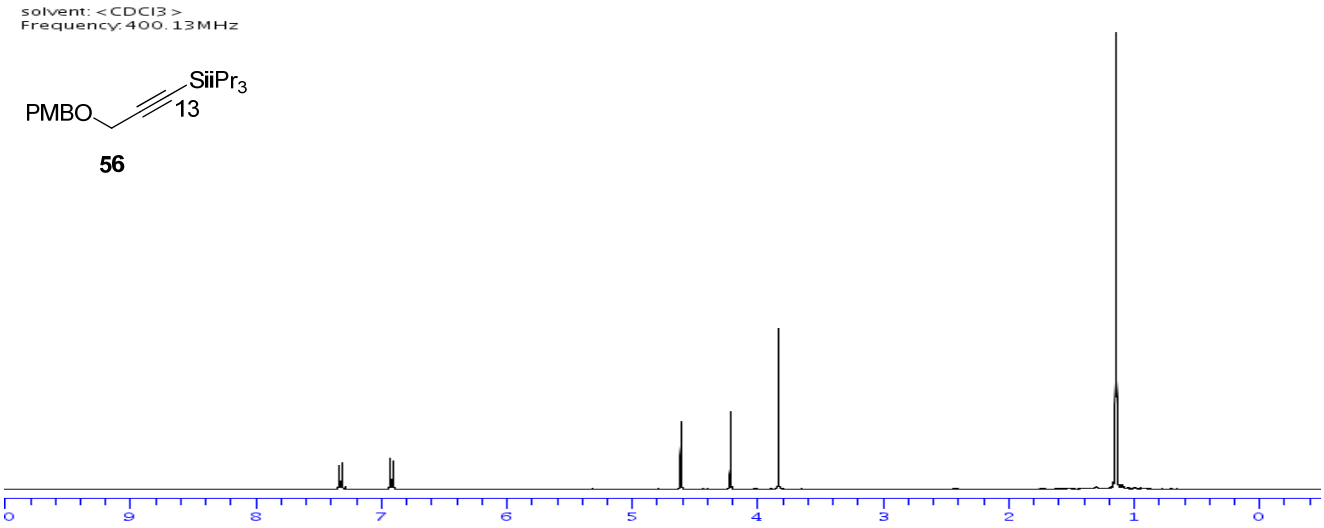
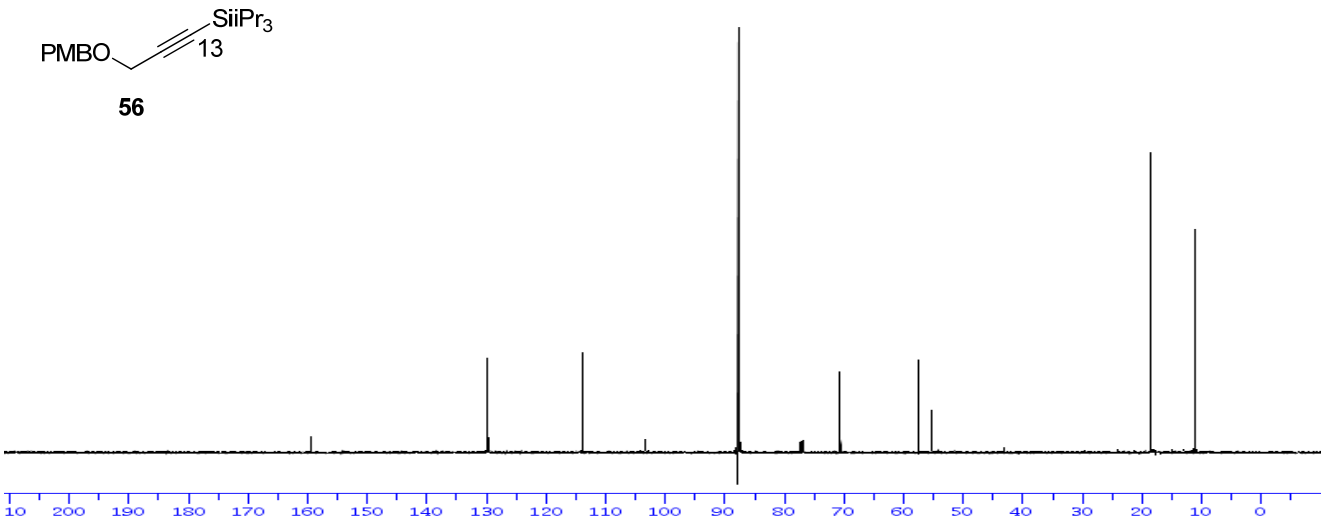
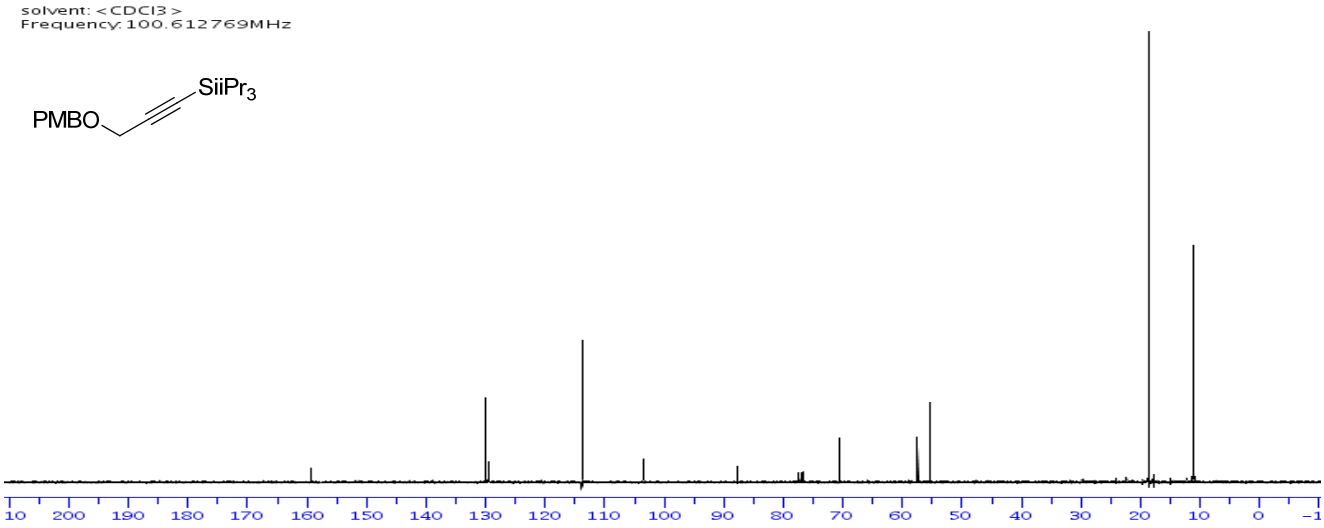



solvent: <CDCl3>
Frequency: 400.13MHz
PMBO
SiiPr3
13
56
0
9
8
7
6
5
4
3
2
1
0


PMBO
SiiPr3
13
56
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


solvent: <CDCl3>
Frequency: 100.612769MHz
PMBO
SiiPr3
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200
190
180
170
160
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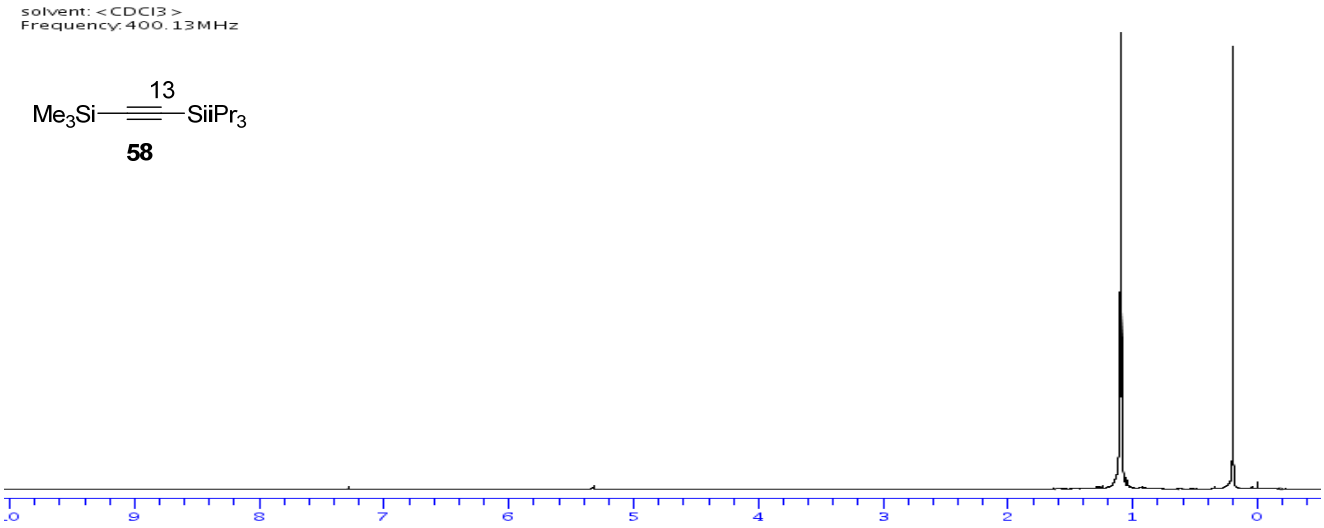
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1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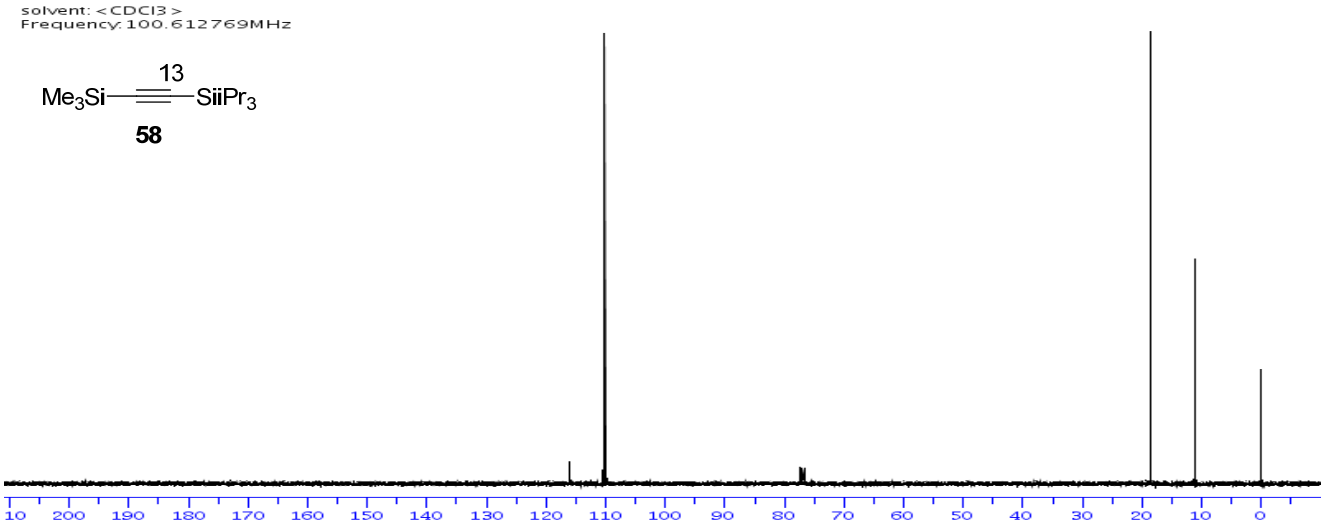
Frequency: 400.13MHz
13
Me3Si
SiiPr3
58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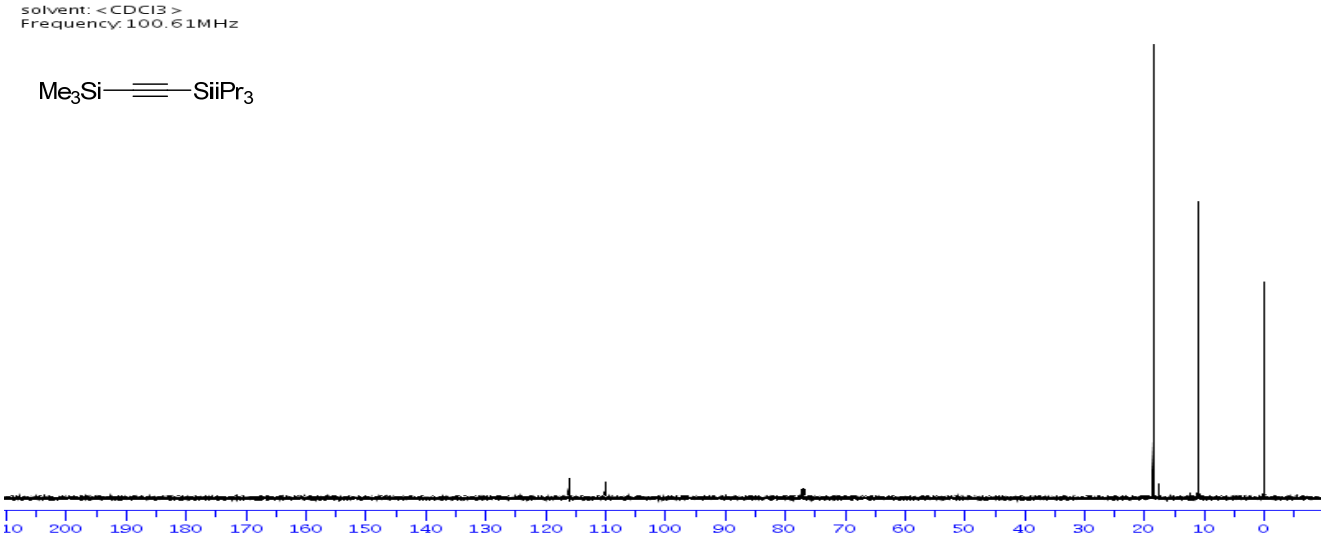
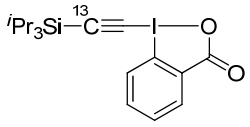
Frequency: 100.612769MHz
13
Me3Si
SiiPr3
58


solvent: <CDCl3>
Frequency: 100.61MHz
Me3Si
SiiPr3

solvent: <CDCl3>
Frequency: 400.13MHz



18

solvent: <CDCl3>
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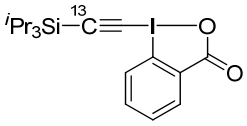
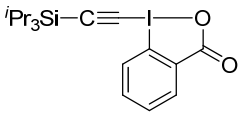


18

solvent: <CDCl3>
Frequency: 100.61MHz



1